(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 538 913 A1**

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: **92122176.8**

(22) Date of filing: **22.06.89**

(51) Int. Cl.5: **A61L 27/00**, A61K 6/033, A61L 25/00

This application was filed on 30 - 12 - 1992 as a divisional application to the application mentioned under INID code 60.

(30) Priority: **10.08.88 JP 200617/88**

(43) Date of publication of application: **28.04.93 Bulletin 93/17**

(60) Publication number of the earlier application in accordance with Art.76 EPC: **0 389 629**

(84) Designated Contracting States: **DE FR GB NL**

(71) Applicant: **NITTA GELATIN INC.**
8-12, 1-chome, Honmachi
Chuo-ku Osaka 541(JP)

(72) Inventor: **Oonishi, Hironobu**
2-6-23, Huminosato, Abeno-Ku
Osaka-shi, Osaka 545(JP)
Inventor: **Sugihara, Fumihito**
393, Ohmachi
Kishiwada-shi, Osaka 596(JP)
Inventor: **Ishii, Takashi**
Room 302 Apple-Tennoji, 3-7-2, Daido, Tennoji-ku
Osaka-shi, Osaka 543(JP)
Inventor: **Suzuki, Kaneo**
167-11, Ishiharado-cho
Kashihara-shi, Nara 634(JP)
Inventor: **Hata, Seiko**
3-14-13, Satsukino-nishi, Mihara-cho
Minamikawachi-gun, Osaka 587(JP)
Inventor: **Takano, Toshikazu**
3-18-7-110, Tatsuno-minami, Sangô-cho
Ikoma-gun, Nara 636(JP)

(74) Representative: **Pacitti, Pierpaolo A.M.E. et al**
Murgitroyd and Company 373 Scotland Street
Glasgow G5 8QA (GB)

(54) **Hardening material for medical and dental use.**

(57) This invention relates to a hardening material for medical and dental use, in which at least either one of α-tricalcium phosphate and/or tetracalcium phosphate is an essential component.

Since the hitherto-known hardening material for medical and dental use, in which α-tricalcium phosphate and/or tetracalcium phosphate are essential components, have used an aqueous solution of one kind of organic acid as a setting solution, it was difficult to safisfy working efficiency for kneading as well as time necessary for hardening. Thus, the subject of this invention is to provide a hardening material for medical and dental use by which the working efficiency for kneading and the time necessary for hardening are satisfied.

To solve said subject, the hardening material for medical and dental use relating to this invention involves, as a hardening adjuster, use of the following: (a) tannin and an organic acid, or (b) at least two kinds of organic acids.

Rank Xerox (UK) Business Services
(3.10/3.5x/3.0.1)

[Technical Field]

This invention relates to hardening material for medical and dental use (hereinafter simply referred to as ┌hardening material ┘) which is used for bone cement, cement for dental use, and root canal sealing material.

[Background Art]

For cement for dental use in recent years, as powder, hydroxyapatite (hereinafter referred to as ┌ HAp ┘) and α-tricalsium phosphate [α-$Ca_3(PO_4)_2$: hereinafter referred to as ┌ α-TCP ┘] has been used and, as a setting solution, an aqueous solution of polyacrylic acid has been used. A hardened product is made with mixing and kneading of the powder with the setting solution. However, polyacrylic acid, which did not react in the hardening, sometimes remains and thus, there exists a problem that a body may suffer damage due to elusion of the acid.

Also, for the cement for dental use and the root canal sealing material, there have been known cement and root canal sealers in a series of zinc oxide eugenol in which eugenol is mixed to a setting liquid with a purpose of a pain-killing effect. However, cell toxicity has been reported with eugenol and also, a composite resin, that is a material for recovery of a tooth crown part, is disturbed in polymerization with eugenol. Therefore, there exist a number of problems for the materials for dental use in the eugenol series.

There has so far been marketed bone cement, in which a polymer material such as polymethylmethacrylate (PMMA) and methylmethacrylate (MMA) is used. However, the following three problems have been known for the bone cement, in which a polymer material is used. At first, a bone tissue in a host side, which is subjected to plugging up, does not directly combined with the bone cement and, when the bone cement is plugged up in a living body for a long period, there exists a problem such as loosening due to interposition of a fibril tissue. At the second, since temperature raises to 90 ~ 100 °C with heat-generation during hardening, there exists a problem that surrounding cells is led to death. At the third, there exists a problem that elusion of a monomer or an oligomer which has not reacted gives a bad effect on a bone.

On the other hand, there have been proposed a number of hardening materials which are furnished with α-TCP powder or tetracalcium phosphate powder ($Ca_4(PO_4)_2O$: hereinafter referred to as ┌ 4CP ┘), which are substances analogous to HAp that is a main inorganic component of a body hard tissue, and also furnished with a setting liquid composed of a solution of a kind of organic acid. For example, in a Japanese official patent provisional publication of Showa 60-36404, there is described a material furnished with the α-TCP powder and a setting solution of 1 M tannic acid. In a Japanese official patent provisional publication of Shown 62-12705, there is described a material furnished with the α-TCP powder and a 30~60 % (w/w) aqueous solution of citric acid. Also, in a Japanese official patent provisional publication of Showa 62-83348, there is described a material furnished with the α-TCP powder and a 45 % (w/w) aqueous solution of hydroxysuccinic acid. The α-TCP and 4-CP are of high chemical reactivity and can be converted into HAp under the conditions similar to those in a body or a mouth.

The hardening materials described in the above publications have such properties as almost no damage for a body, capability to form a hardened product analogous to a body hard tissue, and capability to combine with a hard tissue. A hardening material furnished with α-TCP or 4CP as a powder component and with a solution of an organic acid as a setting liquid component is very useful for medical and dental use, so that its practical use is very exceptable.

Said hardening materials and their hardened products show no damage for a body, but if a ratio between calcium phosphate powder and a setting solution (hereinafter simply referred to as ┌ powder: liquid ratio ┘) becomes larger, time for hardening becomes extremely short, so that there exists a problem that practical use is not possible.

Hardening materials are classified, for example, in the undermentioned major two classes (a) and (b).

(a) Sealing agent . . . The position for use is the one where very great force does not operate, and the agent is used for plugging up and blocking up a lost gap or as a firmly fixing supporter, and the time for hardening of the agent is very long. The agent does not show so high values in properties of the hardening materials, especially, in resisting force against crashing and it is preferred if the agent slowly releases a substance which has a pain-killing effect. For example, it is a bone sealer or a root canal sealer etc.

(b) Cement . . . The position for use is the one where a definite weighting operates, and the agent is used for plugging up and blocking up a lost gap or with a purpose of conjugation of a body hard tissue one another, conjugation between a body hardening tissue and other material, or between other materials

themselves. When an user is going to mix the agent and knead, the time for hardening is properly short and thus, the hardening proceeds in relatively short time and, after hardening, the agent shows a definitely high value in material properties, especially, in resisting force against crashing and it is preferred if it could firmly make a chemical bond with a body hard tissue. The examples are bone cement, cement for dental use, and an adhereing agent for dental use.

According to the above consideration, the present invention has an object to provide a hardening material which can be applied for the sealer described in the above (a) and/or the cement described in (b), undergoes hardening under about room temperature or body temperature, has no injurious character for a body, and besides, has properties of formation of a hardened product analogous to a body hard tissue and of conjugation with a body hard tissue, and also whose time for hardening is freely controlled without lowering working efficiency for mixing and kneading.

[Disclosure of Invention]

The hardening material relating to the present invention is at first characterized by that, to solve the above-described subjects, calcium phosphate powder containing at least either one of α-TCP and 4CP is involved as an essential component and, at least one compound selected from tannin or tannin derivatives is used as a hardening adjuster.

The hardening material relating to the present invention is at the second characterized by that, to solve the above-described subjects, calcium phosphate powder containing at least either one of α-TCP and 4CP is involved as an essential component and, at least one compound selected from tannin and tannin derivatives and at least one compound from collagen and collagen derivatives are used as a hardening adjuster.

The hardening material relating to the present invention is at the third characterized by that, to solve the above-described subjects, calcium phosphate powder containing at least either one of α-TCP and 4CP is involved as an essential component and, at least one compound selected from collagen and collagen derivatives and one kind or more of organic acid are used as a hardening adjuster.

The hardening material relating to the present invention is at the fourth characterized by that, to solve the above-described subjects, calcium phosphate powder containing at least either one of α-TCP and 4CP is involved as an essential component and, at least one compound selected from tannin and tannin derivatives, at least one compound from collagen and collagen derivatives, and one kind or more of organic acid are used as a hardening adjuster.

The hardening material relating to the present invention is at the fifth characterized by that, to solve the above-described subjects, calcium phosphate powder containing at least either one of α-TCP and 4-CP is involved as an essential component and, at least one compound selected from tannin and tannin derivatives and one kind or more of organic acid are used as a hardening adjuster.

Furthermore, the hardening material relating to the present invention is at the sixth characterized by that, to solve the above-described subjects, calcium phosphate powder containing at least either one of α-TCP and 4CP is involved as an essential component and, at least two kinds of organic acids are used as a hardening adjuster.

Hereinafter, the present invention is explained in detail.

The hardening material relating to the present invention is composed of combination of, at least, calcium phosphate powder and a setting liquid.

At least either one of α-TCP and 4CP takes a part or a whole of the calcium phosphate powder. A residual part of the powder is taken by HAp, apatite carbonate, β-tricalcium phosphate (hereinafter referred to as 「 β -TCP 」), and calcium hydrogen phosphate dihydrate etc. The calcium phosphate powder is, in a preferred case, 4CP in its 10 ~ 100 % (w/w), α-TCP in 0 ~ 90 % (w/w), and HAp in 0 ~ 30 % (w/w). If 4-CP is less than 10 % (w/w) of the calcium phosphate powder, there may take place such a problem that, after mixing and kneading, physical strength of a hardened product becomes extemely low. If HAp is more than 30 % (w/w) of the calcium phosphate powder, the time for hardening becomes short and there may take place such a problem that mixing and kneading is not enough. The 4-CP is more reactive than α-TCP, thereby the pot life becomes short and handling becomes difficult and thus, suppression of its reactivity is carried out by adding α-TCP. Also, in the calcium phosphate powder it is preferred that the 60 ~ 100 % (w/w) is α-TCP and the 0~ 30 % (w/w) is HAp. In a case of that α-TCP is less than 60 % (w/w) of the calcium phosphate powder, there may take place a problem that, after mixing and kneading, physical strength of the hardened product become extremely low. If the calcium phosphate other than α-TCP and HAp is more than 10 % (w/w) of the powder, the hardening may be insufficient, or there may take place a problem that the time for hardening becomes short and the mixing and kneading can not be performed

sufficiently. Furthermore, the components other than 4CP, α-TCP, and HAp are preferred to be 40 % (w/w) or less of the calcium phosphate powder. If these components exceed the percentage, physical strength of the mixed and kneaded, hardened product may become extremely low.

Also, if any powder other than said calcium phosphate does not disturb a reaction, replacement by 30 % (w/w) of the total powder agent is possible with the powder. The powder other than calcium phosphate is, for example, a barium salt, a bismuth salt, a zinc salt, and these oxides, which are for addition of a X-ray contrast character, or a dye such as β-carotin, a pigment such as titanium dioxide, or a fluoride such as calcium difluoride. As far as the powder does not participate in reaction or does not give bad effects on physical properties, all kinds of powder which are replacable with a purpose other than these are concerned.

The powder is preferred if it has an average particle diameter of 1 ~ 25 μm. If the average particle diameter of the powder is less than 1 μm, there may take place a problem that, although physical strength of the hardened product increases, the time for hardening time becomes short. If it is more than 25 μm, especially in a case of that it is used for cement for dental use, there sometimes takes place a problem that the film thickness of the hardened product does not become 30 μm or less.

The 4CP is obtained, for example, by baking followed by pulverizing a composition of γ -$Ca_2P_2O_7$ and $CaCO_3$ in a 1 : 2 molar ratio at a temperature of 1300 °C or more, but also the one obtained from other methods can be used. The α-TCP is obtained, for example, by baking followed by pulverizing a composition of γ -$Ca_2P_2O_7$ and $CaCO_3$ in an equal molar ratio at a temperature of 1200 °C or more, but also the one obtained from other methods can be used. The HAp etc. may be calcium phosphate originated from a living body as well as powdered bone or may be a synthetic HAp, apatite carbonate, or β-TCP etc. obtainable from a well-known method or a method known in public. Calcium phosphate of these kinds has no injurious character for a body.

As a setting solution, for example, is used a solution of an organic acid or a body-relating substance. As the body-relating substance is used at least one kind of compound selected from a group of tannin, tannin derivatives, and body-relating organic acids. All of tannin, tannin derivatives, and said body-relating organic acids are substances relating to a body, so that they have no injurious character for a body.

As the tannin, for example, tannic acid is used. The tannin derivatives mean metal salts of tannic acid (for example, tannic acid zinc salt and tannic acid alluminium salt), tannic acid albumin, pyrogallol, and the like. As the tannin and tannin derivatives, any kind can be used. Hereinafter, although tannin is explained as an example, the tannin derivatives can be used in the same way. Tannin is, in comparison with hitherto known setting agents, very slow in hardening rate and also, it is a setting agent, where working efficiency in the mixing and kneading does not almost decrease, that is a hardening adjuster. Also, if tannin is used for a hardening material for dental use, a healing effect on inflammation in the oropharynx and pharynx mucous membrane can be expected due to slow release of a constant concentration of tannin from a hardened product, and a preventive effect on a carious tooth can be expected due to prevention of dissolution of the tooth protein. The tannin concentration in a tannin solution is not especially limited, but when the slow releasing of a constant concentration of tannin is considered, a range of 0.1 ~ 70 % (w/w) is preferred, a range of 0.1~30 % (w/w) is preferred under a condition of coexistence of an organic acid, a range of 0.1 ~ 20 % (w/w) is preferred under a condition of coexistence of collagen, and a range of 0.1 ~ 10 % (w/w) is preferred under a condition of coexistence of an organic acid and collagen. If belower than these ranges, there are a case that a delay effect on hardening is not displayed and a case that slow release of a constant concentration of tannin from the hardened product can not take place. If upper than these ranges, there is a case that the hardened product may collapse in an aqueous solution.

As the organic acid, is used an acid of one kind by alone or an acid mixture of two or more kinds, which is selected from a group of organic acids relating to a living body such as, for example, citric acid, hudroxysuccinic acid, malonic acid, glyceric acid, and glutaric acid. These organic acids give a hardened product of hard quality by being mixed and kneaded with the calcium phosphate powder. Concentration of the organic acid in am organic solution is not especially defined, but a range of 0.1~ 90 % (w/w) is preferred and, under a condition that tannin coexists, a range of 0.1~ 90 % (w/w) is preferred and, under a condition that collagen coexists, a range of 0.1 ~ 70 % (w/w) is preferred and, under a condition that tannin and collagen coexist, a range of 0.1~ 70 % (w/w) is preferred. If belower than these ranges, after mixing and kneading, the hardened product extremely lowers in physical strength and may sometimes collapse in an aqueous solution and, if upper than the ranges, crystals sometimes separate from the setting solution before mixing and kneading.

In the present invention, collagen and/ or collagen derivatives (hereinafter simply referred to as 「 collagen 」) are used as powder or in a melted state. This choice is properly carried out according to a procedure. In any case, when a powder component and a liquid component is mixed and kneaded, it is

preferred for the collagen that it once dissolves and fibrillation takes place accompanied with hardening. If collagen has already coverted into fibrils when it is mixed and kneaded, there may occur a problem that the fibrils separate.

In a case that collagen is used in a melted state, collagen can be used by dissolving it into said setting solution or it can be used by preparing a collagen solution other than a setting solution. When collagen is dissolved, an aqueous solution is prepared by dissolving it into water or into a setting solution of dilute concentration. In a case that collagen is used in a powder state, it may be used by mixing with said calcium phosphate powder or by separating from the calcium phosphate powder.

The proportion for use of collagen is preferred to be 0.02 ~ 100 parts by weight against 100 parts by weight of the calcium phosphate powder. If the proportion for use of collagen deviates from this range, there sometimes occurs a problem that a chemical bond on an interface between a coagulated, hardened product and a body hard tissue becomes weak or the mixing and kneading operation becomes difficult.

As collagen, are used one kind or two kinds or more selected from collagen treated with alkali, collagen made soluble with neutral salts, collagen made soluble with enzyme, and derivatives of these collagens.

A kind of collagen generally undergoes fibrillation within a very short time under physiological conditions (for example, pH 7.0 ~ 7.4, temperature of 36 ~ 37 °C, salt concentration of 0.14 M). Accordingly, if such kind of collagen is used as a hardening adjuster, collagen which has converted into fibrils coagulates and sometimes separates from a calcium phosphate-coagulated product. If this separation takes place, a complex derived from a chemical binding of HAp with collagen can not be obtained. Thus, to obtain this complex, collagen which does not undergo fibrillation within a short time is preferred for use. However, if the collagen species have this character, they are not limited to the type I collagen and, the type II , III , and IV collagens also can be used. Said very short time means 8 minutes, or more preferably about 10 minutes.

As collagens which do not undergo fibrillation under the phsiological conditions, there are, for example, decomposed gelatin (water-soluble gelatin or gelatin 21, products of Nitta Gelatin Inc.), type IV collagen (type IV collagen produced by Collagen Corporation), collagen made soluble with neutral salts (type I collagen), collagen treated with an alkali (type I collagen), succinated collagen (type I collagen), and methylated collagen (type I collagen). Also. as collagens which undergo fibrillation under the phisiological conditions within 8 minutes, there are cited Cellmatrix type I -A produced from Nitta Gelatin Inc. and Cellgen I -AC produced from Kouken Co., LTD. [both are collagens soluble in an acid (type I collagen)] and so on. As collagens which undergo fibrillation with a time longer than 8 minutes, there are cited, for example, atterocollagen (type I collagen: Cellmatrix LA produced from Nitta Geratin Inc., Cellgen produced from Kouken Co., LTD., Vitrogen-100 produced from Collagen Corporation and so on.), collagen soluble in an enzyme (type I collagen : Cellmatrix type I -P produced from Nitta Geratin Inc. and so on.), type II collagen (Cellmatrix Type II produced from Nitta Geratin Inc. and so on.), type III collagen (Cellmatrix type III produced from Nitta Geratin Inc. and so on.), type IV collagen (Cellmatrix type IV produced from Nitta Geratin Inc. and so on.). In this invention, these kinds of collagens can be used with proper selection.

In a case that collagen is used in this invention, not only fibrillation of collagen, but also coagulation and hardening of calcium phosphate proceed in parallel or almost in parallel, and a hardened product derived from coalescence of collagen fibrils and a calcium phosphate-hardened product into one body can be obtained. With these, the hardened product obtained makes a sufficient chemical bond with a body hard tissue.

As collagen, atterocollagen is favored for use. Aterocollagen is, for example, collagen in which a part or a whole of teropeptide at a terminal end of the molecule is removed by treatment with an enzyme and it has no injurious character for a body. Collgen may be used by dissolving it in a setting solution, as a solution independent of the setting solution, or in a powder state. Although the collagen concentration in a collagen solution is not especially limited, it is preferred to be in a range of 0. 01 ~ 35 % (w/w), under a condition of coexistence of an organic acid, preferred to be in a range of 0.05 ~ 35 % (w/w) and, under a condition of coexistence of tannin, preferred to be in a range of 0.01 ~ 30 % (w/w), and under a condition of coexistence of an organic acid and tannin, preferred to be in a range of 0.01 ~ 30 % (w/w).

If belower than these ranges, a delaying effect on hardening by collagen and tannin may not be displayed. If upper than these ranges, collagen may decompose in a solution of an organic acid before mixing, or viscosity of the solution may be overraised. In a case that collagen is used in a powder state, that having the forementioned average particle diameter is favored due to the above reason. As said collagen derivatives, are cited, for example, gelatin, decomposed gelatin (or polypeptide), succinated collagen, and methylated collagen.

In the present invention, proceeding of a hardening reaction of calcium phosphate powder is adjusted by that, at least one kind selected from a group of tannin, tannin derivatives, collagen, collagen derivatives,

and organic acids is used. With this, operation efficiency for kneading is improved, a ratio of powder to liquid can be raised, and a hardened product of higher strength can be obtained. Also, in an use requiring relatively long time for sealing, for example, as root canal sealer for filling a cavity in a tooth root canal, it can be used. Besides, the delaying effect on hardening is greater in a combined use of both tannin and collagen than an use of each one.

The hardening adjuster relating to the present invention refers to the undermentioned (I) and (II).

(I) A compound which, by combining with at least either one of α-TCP and 4CP as well as water, undergoes hardening with very longer time (for example, one hour or more), compared with a setting solution which is so far used and composed of only an organic acid, and does not lower operation efficiency for kneading.

(II) Rather than in a case that the hardening is carried out by using at least one either of α-TCP and 4CP, water, and one or more additional compound, in the case that the hardening is carried out by using further one additional compound (that is, in total, two or more kinds of compounds) the time for hardening can be controlled without lowering operation efficiency for kneading. In this case, said two or more kinds of compounds.

Let the hardening adjuster of said (II) explain in more detail. When said additional one kind of compound is added, the compound which is replaced in a result may be α -TCP, 4CP, water, or other components which are able to constitute a hardening material. When said additional one kind of compound is replaced with any other component constituting a hardening material, it is required that the time for hardening can be controlled, after replacement more than before replacement, without lowering the operation efficiency for kneading. For example, when tannic acid is added to a system in which the powder agent is a 100 % of α -TCP and the liquid agent is 35 % of citric acid and 65 % of water, if in any of the following ① ~ ③ method the time for hardening is delayed with addition of tannic acid, the citric acid and tannic acid are called as a hardening adjuster.

① Five parts in the 100 parts of α-TCP are replaced with tannic acid.

② Five parts in the 65 parts of water are replaced with tannic acid.

③ Five parts in the 35 parts of citric acid are replaced with tannic acid.

As shown in Fig. 5 (c), citric acid and malic acid are hardening adjusters in the case that citric acid and malic acid are in combined use. When total concentration of the organic acids is constant (for instance, 45 %), if proportion of malic acid to a sum of malic acid and citric acid is equal to 0.5 or more, the time for hardening becomes longer than a case that citric acid alone is used. Also, in a solution of malic acid alone, if water is replaced with citric acid, the hardening time becomes longer than a case that malic acid alone is used. Further, in a solution of citric acid alone, if water is replaced with malic acid, the hardening time becomes longer than a case that citric acid alone is used under a condition that concentration of citric acid is 9 % or less. In Fig. 5 (c), the broken line shows congelation time in a case that malic acid in a 45 % (a sum of citric acid and malic acid) solution is replaced with water and one point-dotted chain line shows congelation time in a case that citric acid in a 45 % (a sum of citric acid and malic acid) solution is replaced with water.

As shown in Fig. 6, citric acid and malonic acid are hardening adjusters in a case that citric acid and malonic acid are in combined use. When total concentration of the organic acids is constant (for instance, 45 %), the congelation time becomes longer than a case that citric acid alone is used. Also, if water is replaced with citric acid in a solution of malonic acid alone, or if water is replaced with malonic acid in a solution of citric acid alone, the congelation time becomes longer in both the cases. In Fig. 6, the broken line shows the congelation time in a case that malonic acid in a 45 % (a sum of citric acid and malonic acid) solution is replaced with water, and the one point-dotted chain line shows the congelation time in a case that citric acid in a 45 % (a sum of citric acid and malonic acid) solution is replaced with water.

In the case that said hardening adjuster provides hardening material, an essential reason is as follows.

When there is a hardening material composed of α-TCP and/ or 4CP, water, and one kind of organic acid (for example, an aqueous solution composed of 100 % of α-TCP and an aqueous 45 % solution of citric acid), two methods are considered as the ones to delay the hardening without use of a hardening adjuster. The first one, as seen in Fig. 7 (c), is a method in which concentration of a solution is raised (that is due to replacement of water by an organic acid), but this method requires increasing force for kneading as concentration of the organic acid increases, so that there is a deficiency that it becomes very bad in efficiency for operation. The second one, as shown in each (c) of Fig. 8 ~ Fig. 12, is a method in which a ratio of powder to liquid is lowered (the liquid proportion is raised) (that is due to replacement of calcium phosphate powder with water and an organic acid), but this method shows decreasing strength as a ratio of powder to liquid becomes lower and thus, there is a weak point that physical properties of the material becomes very low after hardening, for example, an increase of decomposition percentage. To delay

the hardening with compensating for these weak points (lowering of operation efficiency during kneading and of physical properties after hardening), there is required the above-described hardening adjuster.

Powder agent and/or setting liquid in hardening materials in the present invention may be used with addition, if neccesary, of any one or more selected from polysaccarides such as arginic acid, carrageenan, pectin, xanthane gum, locustbean gum, and jellan gum, which converts into a gel by a calcium ion, and mucopolysaccharid e, chitin, and chitosan. Also, to add viscosity during operation and thereby, to improve operation efficiency, as an adhering agent for said powder agent and/or setting liquid, polyalkylene glycol, polyethylene glycol, polyvinylalcohol, polyvinylpyrrolidone, and dextran and so on may be added in a degree of that they do not participate in reaction or do not affect badly on the physical properties.

The hardening materials in this invention are able to undergo hardening by mixing and kneading at about room temperature or temperature of a living body and thus, there is no problem of cell death by generating reaction heat.

The hardening materials in the present invention, for example, are as follows.

① A system composed of combination of calcium phosphate powder and tannin.

As materials in this system, tannin is a hardening adjuster and used as a tannin solution. The hardened product is also a slow releasing material of tannin. Although the ratio of powder to liquid for materials in this system is not especially limited, a range of 0.1 ~ 5 g /mℓ is preferred. If belower than this range, the hardening may become unsufficient, and if upper than the range, the kneading under room temperature may become unsufficient.

A reaction mechanism for materials in the ① system is considered, for example, as follows on the basis of analysis data by X-ray powder diffraction, infrared absorption spectra, and scanning electron microscope. When calcium phosphate powder and a tannin solution is mixed and kneaded at room temperature or around living body temperature, octacalcium phosphate [$Ca_8H_2(PO_4)_6 \cdot 5H_2O$: hereinafter referred to as 「 OCP 」] is formed by coordination of water to 4CP in the powder. Also, in a case that α-TCP is contained, by coordination of water with this, noncrystalline calcium phosphate [$Ca_3(PO_4)_2 \cdot nH_2O$: hereinaf ter referred to as 「 ACP 」] is formed. On the other hand, tannin forms an associated material, which is considered as fibril-like. The OCP and ACP cohere with the tannin-associated material and, under this condition, the hardening progresses with conversion of OCP and ACP into HAp.

② A system composed of combination of calcium phosphate powder, tannin, and collagen.

In the materials in this system, tannin and collagen are hardening adjusters. Also, tannin works on collagen for crosslinking. The hardened product from the materials in this system becomes a slow releasing material of tannin. Since collagen is contained, affinity with a living body tissue in the neighborhood is excellent. Collagen may be used by preparing a solution independent of the tannin solution, by dissolving it in the tannin solution, or by its powder state.

Although proportion for use of the materials in this ② system is not especially limited, a range of 0.01 ~ 20 parts by weight of tannin and a range of 0.01 ~ 20 parts by weight of collagen against the 10 ~ 80 parts by weight of calcium phosphate powder are preferred. If tannin is belower than the range, there may be cases that the hardening becomes unsufficient or slow release of constant concentration of tannin from the hardened product is impossible, and if upper than the range, the calcium phosphate powder is sometimes not sufficiently kneaded during kneading operation. If collagen is belower than the range, the strength of the hardened product is sometimes too low, and if upper than the range, there may be a case that sufficient kneading is not possible.

A reaction mechanism of the ② system is considered, for example, as follows on the basis of analysis results from X-ray powder diffraction, infrared absorption spectra, and scanning electron microscope and so on. When calcium phosphate powder, a tannin solution, and collagen are mixed and kneaded at room temperature or around living body temperature, OCP is formed with coordination of water to 4CP in the powder and, in a case that α-TCP is contained, ACP is formed with coordination of water to α-TCP. On the other hand, is formed a complex having a structure derived by crosslinking between collagen and tannin. The hardening progresses by that HAp, which is converted from OCP and ACP, crystallizes and coheres to the forementioned complex, which is considered as fibril-like.

When the materials in the ① and ② systems, each of those is mixed and kneaded as described above, the hardening progresses very slowly than a case that an organic acid is used as a hardening agent, and a hardened product of soft quality is obtained. For example, the hardening completes within about 1 ~ 2 days after initiation of kneading at room temperature or around living body temperature. Because of this,

the materials in the ① and ② systems, for example, can be used as a root canal sealer for filling cavity in root canal.

③ A system composed of combination of a calcium phosphate powder, an organic acid, and collagen.

In this system also, an organic acid and collagen are hardening adjusters. Collagen may be used by preparing a solution independent of an organic acid solution, by dissolving it into an organic acid solution, or in a powder state.

Although proportion for use of materials in the ③ system is not especially limited, a range of 5 ~ 70 parts by weight of an organic acid and a range of 0.01 ~ 30 parts by weight of collagen against the 30 ~ 80 parts by weight of calcium phosphate powder are preferred. If the organic acid is below than the range, the hardening sometimes becomes unsufficient, and if upper than the range, a delaying effect of collagen on hardening is not sometimes displayed. If collagen is below than the range, strength of the hardened product is not sometimes enhanced, and if upper than the range, kneading under room temperature is not sufficiently possible.

A reaction mechanism of materials in the ③ system is considered, on the basis of analysis results from X-ray powder diffraction, infrared absorption spectra, and scanning electron microscope, for example, as analogous to a collagen-calcified model of a living body hard tissue, as follows. When calcium phosphate powder, an organic acid, and collagen are mixed and kneaded at room temperature or around living body temperature, a chelate bond is formed between calcium atoms of 4CP and α-TCP in the powder and the carboxyl groups in the organic acid and thus, a neutralization reaction progresses. On the other hand, collagen converts into fibrils and the chelated product coheres with the collagen fibrils. Under presence of water and at room temperature or around living body temperature, the chelated products existing on a surface of the hardened product and on a surface of the pores and the unreacted 4CP and α-TCP form OCP and ACP by undergoing a hydration reaction, and then, these OCP and ACP converts into HAp which crystallizes into collagen fibrils, and thereby the hardening progresses.

④ A system composed of combination of a calcium phosphate powder, an organic acid, tannin, and collagen.

The materials in this system involve an organic acid, tannin, and collagen as hardening adjusters. The hardened product from the materials in this system becomes a slow releasing body of tannin. Each of tannin and collagen may be used by preparing a solution independent of an organic acid solution, by dissolving it in the organic acid solution, or by preparing a solution containing both tannin and collagen. Also, collagen may be used in a powder state.

Although proportion for use of materials in the ④ system is not especially limited, a range of 5 ~ 60 parts by weight of an organic acid, a range of 0.05 ~ 10 parts by weight of tannin, and a range of 0.05 ~ 30 parts by weight of collagen against the 30 ~ 80 parts by weight of calcium phosphate powder are preferred. If the organic acid is below than the range, the hardening sometimes becomes unsufficient, and if upper than the range, unreacted organic acid sometimes is eluted in large quantity. If tannin is lower than the range, strength of the hardened product becomes low and, in addition, a delaying effect on hardening is not sometimes displayed, and if upper than the range, there may be a case that kneading under room temperature becomes unsufficient. If collagen is below than the range, strength of the hardened product becomes low and a delaying effect on hardening is not displayed. If it is upper than the range, there are a case that kneading under room temperature becomes unsufficient.

A reaction mechanism of the materials in the ④ system is considered, on the basis of analysis results from X-ray powder diffraction, infrared absorption spectra, and scanning electron microscope, for example, as analogous to a collagen-calcified model for a bone tissue, as follows. When calcium phosphate powder, an organic acid solution, tannin, and collagen are mixed and kneaded under room temperature or around living body temperature, a chelate bond is formed between calcium atoms of 4CP and α-TCP in the powder and the carboxyl groups of the organic acid and thus, a neutralization reaction progresses. On the other hand, is formed a complex (which is considered as fibril-like) constructed by crosslinking of tannin with collagen. The chelated compound coheres to the complex. Under presence of water and at room temperature or around living body temperature, the chelated compound existing on a surface of the hardened product and on a surface of the pores and the unreacted 4CP and α-TCP form OCP and ACP by undergoing a hydration reaction and, these OCP and ACP converts into HAp which crystallizes with said complex, and thus the hardening progresses.

⑤ A system composed of combination of calcium phosphate powder, an organic acid, and tannin.

In this system, an organic acid and tannin are hardening adjusters. The hardened product from materials in this system is a slow releasing body of tannin. Tannin may be used by preparing a solution independent of the organic acid solution or by dissolving it in the organic acid solution.

Although proportion for use of materials in the ⑤ system is not especially limited, a range of 5 ~ 60 parts by weight of the organic acid and a range of 0.01 ~ 10 parts by weight of tannin against the 30 ~ 80 parts by weight of the powder is preferred. If the organic acid is below than the range, the hardening may become unsufficient, and if upper than the range, it is sometimes impossible to knead enough under room temperature. If tannin is below than the range, a delaying effect on hardening is not sometimes displayed and slow release of constant concentration of tannin from the hardened product may not be possible. If upper than the range, it is sometimes impossible to knead enough under room temperature.

A reaction mechanism of the ⑤ system may be considered, on the basis of analysis results from X-ray powder diffraction, infrared absorption spectra, and scanning electron microscope, for example, as follows. When calcium phosphate powder, an organic acid solution, and tannin are mixed and kneaded under room temperature or around living body temperature, a chelate bond is formed between the calcium atoms of 4CP and α-TCP in the powder and the carboxyl groups of the organic acid and thus, a neutralization reaction progresses. On the other hand, tannin forms an association compound (which is considered as fibril-like), with which the chelated product coheres. Under presence of water and at room temperature or around living body temperature, the chelated product and the unreacted 4CP and α-TCP form OCP and ACP by undergoing a hydration reaction and, these OCP and ACP converts into HAp which crystallizes with the tannin association compound, and thus the hardening progresses.

⑥ A system composed of combination of a calcium phosphate powder and two or more kinds of organic acids.

In this system, two kinds or more of organic acids are hardening adjusters. The two or more kinds of organic acids may be used by dissolving those into the same solution or into separate solutions. Composition ratio of the two or more kinds of organic acids is variable with combination of organic acids. For example, as mentioned above it is just as explained with referring to Fig. 5 (c) and Fig. 6.

The hardening materials in said ⑤ and ⑥ systems undergo mixing and kneading of the powder component and the liquid component at a wanted temperature, for example, room temperature to convert those into a slurry or a paste, which are then applied, injected, or plugged up for a treatment part. The slurry and paste undergo a chemical reaction under in vivo environments and thereby, a chelate bond is formed between the calcium atom in α-TCP and the carboxyl group in an organic acid by undergoing a neutralization reaction and thus, the hardening progresses.

Under presence of water and at room temperature or around living body temperature, the chelated products existing on a surface of the hardened product and on a surface of the pores and the unreacted α-TCP yield ACP by undergoing a hydration reaction, where ACP transforms into HAp. The forming hardened product shows a structure similar to a hard tissue of the living body and combines with the hard tissue of the living body. In a case that tannin is used for a hardening material composition, the hardened product is a slow releasing body of tannin.

The hardening materials in said ⑤ and ⑥ systems can be used as a sealing material and an adhesive etc. for the hard tissue of a living body, for examples, a treatment material for periodontosis, a sealing material for root canal, a sealing material for broken bone, and an adhesive for the hard tissue.

When the materials in said ③ ~ ⑤ systems is mixed and kneaded, progress of the hardening becomes slower than a case of that tannin or collagen is not used. For example, at room temperature or around living body temperature the hardening is completed during 5 ~ 60 minutes after initiation of the kneading and a hardened product of hard quality is obtained. Because of this, the ratio of calcium phosphate powder to an organic acid can be raised, so that strength of the hardened product can be increased. In particular, if collagen is used, without raise of the ratio of calcium phosphate powder to an organic acid the compression strength increases and, in addition, after said hardening is completed, the compression strength increases with time passage and elasticity is enriched. The materials in said ③ ~ ⑤ systems can be used as sealing, bonding, or dental prosthesis materials for the hard tissue of a living body, for examples, bone cement and cement for dental use and so on.

When a hardening product at an initial stage obtained from mixing and kneading of the materials in said ③ ~ ④ systems is immersed in a physiological PBS (phosphate-buffered saline) at 37 °C, the resisting force for crushing increases with time passage. That is, when the materials in said ④ and ⑤ are used as

bone cement, the strength increases with time passage even after they are buried. This is considered due to the use of collagen.

When the materials in said ③ ~ ⑥ systems are converted into bone cement and then buried in bone of a living body, since the cement is active for the living body and thus, it takes a bone-like structure and coalesces into one body with a bone tissue. In a case that α-TCP is used, since α-TCP is biodegradable, it can be gradually substituted by a new bone during a period from 6 months to 1 year. That is, in the hardening materials relating to the present invention, when is used as bone cement a material in which am organic acid is used as a setting agent and at least either one of tannin and collagen is used as a hardening adjuster, the material is after being buried substituted by a bone tissue with time passage and thus, coalesces into one body with an already existing part.

Besides, all the materials in said ① ~ ⑥ systems are possible to contain any material other than the above-described materials as far as the purpose attainment in the present invention is not disturbed.

Also, the use is not limited within said examples.

All the materials in said ① ~ ⑥ systems, because a setting agent is used therein, can control the time length for hardening without lowering operation efficiency for kneading. Incidentally, in a case that the hardening materials in this invention are for bone cement or dental cement and so on, it is preferred to take such compoment composition as the undermentioned (i)~ (iv) . This is, as mentioned later, because strength and disintegration of the hardened product as well as time for hardening is within a range suitable for practical use. Among the undermentioned (i) ~ (iv) hardening materials, (i) and (ii) are included in the materials of said ⑤ system and (iii) and (iv) are included in the materials of said ⑥ system.

(i) A hardening material in which α-TCP, an organic acid, and water are essential components, in composition proportion of said water, the organic acid, and tannic acid the total of the organic acid and tannic acid is 40 ~ 48 % by weight (hereinafter referred to as simplely 「 % 」) and the residual part is water, said organic acid is citric acid and/or malonic acid, and the mutual proportion of citric acid, malonic acid, and tannic acid is 60 ~ 90 parts by weight for citric acid (hereinafter referred to as simply 「 part 」 for part by weight), 0 ~ 35 parts or less for malonic acid, and 30 parts or less for tannic acid against the total 100 parts of these three acids, but when the malonic acid is 0 part, citric acid is 70 ~ 89 parts and tannic acid 30~ 11 parts.

(ii) A hardening material in which α-TCP, an organic acid, and water are essential components, in composition proportion of said water, the organic acid, and tannic acid the total of the organic acid and tannic acid is 40 ~ 48 % and the residual part is water, said organic acid is citric acid and/or malic acid, and the mutual proportion of citric acid, malic acid, and tannic acid are, respectively, 0~ 65 parts, 20 ~ 90, and 15 or less against 100 parts of the total three components.

(iii) A hardening material in which α-TCP, organic acids, and water are essential components, in compostion proportion of said water and the organic acids the organic acids are 40~ 48 % and the residual part is water, said organic acids are citric acid and malonic acid, the mutual proportion of these organic acids is 65 ~ 90 parts for citric acid and 10 ~ 35 for malonic acid against 100 parts of the total organic acids

(iv) A hardening material in which α-TCP, organic acids, and water are essential components, in composition proportion of said water and the organic acids the organic acids are 40 ~ 48 % and the residual part is water, said organic acids are citric acid and malic acid, and the mutual proportion of these organic acids is 10 ~ 65 parts for citric acid and 35 ~ 90 for malic acid against 100 parts of the total organic acids.

In said compostion proportion of water and an organic acid, if the composition proportion of the organic acid is less than 40 % against the total weight amount of both the materials, the hardening becomes so rapid during mixing that the handling becomes difficult, and if exceeds 48 %, the decomposition percentage may become high, the viscosity may become so high that the kneading becomes dificult, or may result in elusion of the unreacted acid which gives an impetus for a living body and cause a inflammatory reaction.

If the mutual proportion for combined use of said organic acids is deviated from said corresponding range, effects due to the combined use can not be obtained.

Hereinafter, the process where the present inventors found the forementioned means for solution is explained in detail.

The present inventors, to solve said subjects, studied the reason why practical use is not carried out and, as a result, found that the hitherto known hardening materials are not satisfactory for all the undermentioned (1)~ (3) capacities and are defective in any of the capacities.

(1) Strength of the hardened product is high.

(2) Under physiological conditions, stability of the hardened product is high and decomposition character is low.

(3) During mixing and kneading, the hardening process proceeds with proper slowness and the efficiency for operation is superior.

The inventors, to be satisfactory for all of these (1)~ (3) capacities and to get superior affinity for the living body hard tissue, carried out studies with consideration that, rather than the use of a calcium phosphate besides α-TCP and an addition of a component other than the organic acid to a setting solution, a superior idea is to use an organic acid which is known, according to the previous research, to have no character injurious for a body and to set its most suitable concentration range.

As organic acids for the hardening materials which are of high possibility for use are known monocarboxylic acids, dicarboxylic acids, and tricarboxylic acids. In particular, the dicarboxylic acids and the tricarboxylic acids in the Krebs cycle are superior complex-forming reagents for calcium and a high possiblity for use is expected. For almost all the monocarboxylic acids and for the dicarboxylic acids, since chelate-forming force is weak, the decomposition percentage of ten raises extremely after the hardening finished (for example, pyruvic acid, glyceric acid, and lactic acid, and also, as a dicarboxylic acid, maleic acid). Also, due to weak chelate-forming force, some acids show long hardening time (for example, the cases of lactic acid and glucuronic acid). Due to weak chelate-forming force, there are acids with which a calcium salt are formed within short time and, as a result, the hardening time becomes extremely short (for example, as a monocarboxylic acid, pyruvic acid and as a dicarboxylic acid, tartaric acid, oxalic acid, and glycolic acid). Although the tricarboxylic acids have relatively strong chelate-forming force and are expected to show very often superior physical properties after the hardening (in strength and decomposition percentage etc.), its majority show poor solubility in water and are hard to obtain suitable concentration (for example, aconitic acid, oxaloacetic acid, and oxalosuccinic acid etc.). Also, among the dicarboxylic acids, some acids show poor solubility (for example, succinic acid and fumaric acid etc.). From consideration of these, the acids of high solubility in water in a group of the di- or tricarxylic acids can be expected to be of practical use. Also, in a group of tannins, since tannic acid shows weak chelate-forming force, its hardening time becomes long, but it was listed for examination because works as a setting agent as described above.

Accordingly, when the acids of no character injurious for a body in a great number of organic acids estimated to be usable as a hardening material, that is, all the organic acids shown in table 1 (tannic acid is included in the organic acids mentioned here) are each used in a form of an independent aqueous solution as a setting solution, was examined whether or not a concentration range which is satisfactory for the above-described (1) ~ (3) capacities can be set. At first, solubilities of the organic acids for water were examined and, as a result, high solubility was shown with circle and poor solubility with cross in table 1. The acids of poor solubility were excluded from the examination list and the acids of high solubility were further examined. The variation of resisting force for crushing (kg f/cm^2) when the citric acid concentration is varied is shown in Fig. 7 (a), the variation of decomposition percentage (%) with the above variation in Fig. 7 (b), and the variation of coagulating time (min.) with the above in Fig. 7 (c). On the basis of these graphs, said concentration range was examined. Other organic acids were also similarly examined.

In table 1, the strength for crusing corresponds to said (1) capacity, the decomposition percentage to said (2) capacity, and the coagulating time to said (3) capacity, respecitvely. These capacities were examined on a basis of JIS T6602 under the conditions that the ratio between powder and liquid was 2.5 and the mixing and kneading were performed with hand-working. Results are presented for each of the capacities by showing with circles if they are practical standard, with crosses if they are definitely unpractical standard, with triangles if they are standard somewhat inferior than the practical standard, and also, by showing with cicles if a concentration range where the three capacities are satisfied in practical standard at the same time is held, and with crosses if it is not held.

Table 1

Kind of organic acid	Solubility in water	Strength for crushing	Decomposition percentage	Coagulating time	Presence of concentration to satisfy three capacities at the same time	Kind of organic acid	Solubility in water	Strength for crushing	Decomposition percentage	Coagulating time	Presence of concentration to satisfy three capacities at the same time
Citric acid	○	○	○	△	×	Pantothenic acid	○	×	×	×	×
Formic acid	○	△	×	×	×	Tartaric acid	○	△	×	×	×
Acetic acid	○	×	×	×	×	Glutamic acid	×	—	—	—	—
Oxalic acid	○	△	△	×	×	Phytic acid	○	△	△	×	×
Lactic acid	○	△	×	×	×	Pyruvic acid	○	○	×	△	×
Tannic acid	○	△	—	×	×	Malonic acid	○	○	△	○	×
Glycolic acid	○	○	△	×	×	Aconitic acid	×	—	—	—	—
Maleic acid	○	×	×	△	×	Gluconic acid	○	×	×	×	×
Itaconic acid	○	△	×	×	×	Glyceric acid	○	×	×	×	×
Fumaric acid	×	—	—	—	—	Succinic acid	×	—	—	—	—
Polyglutamic acid	×	—	—	—	—	Oxaloacetic acid	×	—	—	—	—
Polyasparaginic acid	×	—	—	—	—	Oxalosuccinic acid	×	—	—	—	—
Malic acid	○	○	△	○	×	Glucuronic acid	○	△	△	×	×

As seen in Table 1, all the organic acids so far proposed have not a concentration to satisfy said three capacities all. However, citric acid, malic acid, and malonic acid are in outline satisfactory for said (1) ~ (3) (that is, capacities of the 「 cross 」 mark standard are absent), but it is understood that the other organic acids have a problem in any of the capacities (that is, those of the 「 cross 」 mark standard exist). Also, it is understood that the organic acids differ in effects on said (1) ~ (3) capacities depending upon their kinds. This difference is considered as arising from decarcification ability, rate of chlate-forming reaction

and binding force with Ca^{2+} , and molecular weight of the organic acids, pH and stability with Ca^{2+} of the mixed and kneaded products, and difference of varying percentage in the hardening density.

On the other hand, if the concentration of an organic acid in a setting solution is high, the resisting force for crushing becomes high, the coagulating time tends to be long, the decomposition percentage tends to be high, a considerable amount of force may be needed for the kneading operation, and sealing for a small gap in a living body may become difficult. Futhermore, if the concentration of an acid is high, the acid which did not react may undergo elution, and it gives an impetus to a living body and may cause an inflammatory reaction. On the contrary, if the concentration of an organic acid is low, there is a case that the hardening takes place at a time very early after mixing, and there is a trend that the use becomes difficult. From consideration of these things, it is hoped that the concentration of the organic acid is about 35 ~ 50 %.

Next, the inventors considered to satisfy said (1) ~ (3) not by use of an organic acid by alone, but by use of two kinds or more of organic acids in combination.

Because, it was considered that there may be an organic acid which, even if the only one use is practically useless, shows a possibility of practical use if it is used in combination with an other acid. For example, as mentioned above, when only one acid is used, at least 30 % or more of solubility in water is needed, but even if the organic acid is a tricarboxylic acid or a dicarboxylic acid which is itself of poor solubility, the acid is of sufficiently practical use as one important component when the kind of an acid in combination use is properly chosen and when solubility of the acid itself is 10 % or more. Also, even if it is an organic acid of weak chelate-bonding force whose only one use is practically impossible, it can be used as one of main components in a case of that an organic acid which is used in combination at the same time has a strong chelate-forming force.

Accordingly, by adjusting the total concentration of organic acids at 35 ~ 50 % and by changing proportion of the two kinds of organic acids, whether said (1)~ (3) capacities can be all satisfied or not were examined. By using especially superior three kinds of organic acids (citric acid, malic acid, and malonic acid) selected from said 20 kinds or more of organic acids and by using each of those in combination with another organic acid, it was examined whether the capacity which was displayed in a case of only one acid use has been lost and also, whether the capacity which was not displayed in a case of only one acid use has revealed. These examinations were carried out as the undermentioned.

First, by using two kinds of organic acids in combination, was carried out an operation to exclude the organic acids which make worse the capacity in a case of only one acid use. The examinations were carried out according to the above procedure wherein respective proportion of the organic acids were 90 % for citric acid, malic acid, and malonic acid, that of the other organic acids was the remaining 10 %, and total concentration of the organic acids was 45 %. In result, it was seen that, when the seven kinds of such acids as tannic acid, phytic acid, maleic acid, pyruvic acid, tartaric acid, oxalic acid, and glycolic acid were used in combination with each of citric acid, malic acid, and malonic acid, they did not make worse the capacity which was displayed in a case of only one use of an acid such as citric acid, malic acid, and malonic acid, and also that citric acid, malic acid, and malonic acid did not make worse the capacity which was displayed in a case of only one acid use.

Accordingly, by using in combination a set of two acids selected from the ten kinds of organic acids that are citric acid, malic acid, malonic acid, tannic acid, phytic acid, maleic acid, pyruvic acid, tartaric acid, oxalic acid, and glycolic acid, was examined whether proportion for use (ratio by weight) which increases all said three capacities exists or not. The examinations were carried out according to the above procedure by setting the total concentration of organic acids at 35, 40, 45, and 50 %, respectively. Fig. 5 (a) shows resisting force for crushing in a case of that malic acid and citric acid are used in combination and the total concentration is adjusted at 45 %. Fig. 5 (b) shows decomposition percentages in those cases. Fig. 5 (c) shows coagulating time in those cases. In these combination use, when the proportion for use of citric acid and malic acid was in a range from 10 % vs. 90 % to 50 vs. 50, said (1) ~ (3) capacities were improved in the same degree or more, compared to cases of only one use of the respective acids. Similarly, in other combination use was examined the proportion for use wherein said (1)~ (3) capacities were improved in the same degree or more, compared to cases of only one use of the respective acids.

From these results, there is seen no proportion for use which satisfies all the three capacities in the use of phytic acid, maleic acid, pyruvic acid, tartaric acid, oxalic acid, and glycolic acid. However, if two kinds of acids optionally selected from citric acid, malic acid, malonic acid, and tannic acid are used, there is proportion for use which satisfies all the capacities, as seen in table 2.

Table 2

Total concentration of organic acid in setting solution (weight %)	35	40	45	50
Proportion for use of two kinds of organic acids (%) *1				
citric acid / malic acid	50/50 ~ 30/70	70/30 ~ 20/80 *2	50/50 ~ 10/90 *2	40/60 ~ 20/80
citric acid / malonic acid	95/5 ~ 70/30	95/5 ~ 65/35 *2	90/10 ~ 60/40 *2	90/10 ~ 80/20 *2
citric acid / tannic acid	90/10 ~ 70/30 *2	95/5 ~ 70/30 *2	95/5 ~ 70/30 *2	95/5 ~ 85/15
malic acid / malonic acid	none	90/10 ~ 70/30 *2	90/10 ~ 50/50	none
malic acid / tannic acid	90/10 ~ 70/30	90/10 ~ 70/30	90/10 ~ 80/20 *2	90/10 ~ 85/15
malonic acid / tannic acid	none	80/20 ~ 95/5	90/10	none

*1; proportion for use in a case that, compared to the case of only one acid use, various properties were improved.

*2; those that the results of various properties were especially good.

Next, from said four kinds of organic acids the three kinds were optionally selected and, on a basis of the numeral values in table 2, was examined the proportion for use of the organic acids which is satisfactory for all said three capacities as carried out above. Fig. 4 is for a three components system of citric acid, malic acid, and tannic acid (the total concentration of organic acids is 35 %). For other three components systems were similarly prepared figures. Then, when said three capacities were examined outside the area C surrounded by the line which connects the numeral values of proportion for use in the two components

system, it was found that capacity improvement was not achieved as the parting from the area C increases. From these results, in a case that the three kinds of organic acids are used in combination, it was considered that the proportion for use which is the best to improve said three capacities can be found in an area obtainable from table 2.

On the other hand, the proportion for use wherein said three capacities are especially good is considered, from table 2, to be in a range of that the total concentration of organic acids is 40~ 48 %. Then, the total concentration of organic acids is set at 42.5 % and, in both the proportions for use of 40 % and 45 % in table 2, said three capacities were examined according to the following standards.

(A) A proportion for use in which the resisting force for crushing exceeds 1100 kg f/cm^2. This numeral value is the general which is realized with a hardening material available in a market at present.

(B) A proportion for use in which the decomposition percentage does not exceed 2 %. This numeral value was set to prevent elusion of an unreacted acid toward a living body which may give an impetus and also, to prevent decompositon of hardened products in saliva or body fluids as well as deterioration of its strength within a short time.

(C) A proportion for use in which the coagulation time is in a range of 2.5 ~ 8.0 minutes. This numeral value range is derived from an operation character, when a user carries out the mixing and kneading of a hardening material.

With respect to the three components system of citric acid, malonic acid, and tannic acid, the area D which is satisfactory for said capacity (A) is shown by Fig. 3 (a), the area E which is satifactory for said capacity (B) by Fig. 3 (b), and the area F which is satisfactory for said capacity (C) by Fig. 3 (c), respectively. In Fig. 3, the area G shows a proportion for use derivable from table 2. By being performed similarly in the three components system of citric acid, malic acid, and tannic acid, in the three components system of malic acid, malonic acid, and tannic acid, and in the three components system of citric acid, malic acid, and malonic acid, a proportion for use which is satisfactory for all said capacities (A) ~ (C) is shown in Fig. 1 and Fig. 2. That is, as seen in Fig. 1, in the three components system of citric acid, malonic acid, and tannic acid and, as seen in Fig. 2, in the three components system of citric acid, malic acid, and tannic acid, it is understood that all said capacities (A) ~ (C) are satisfied in only the two systems.

Furthermore, on the optional points in each of the areas A and B shown in Fig. 1 and Fig. 2, when respective capacities were examined by setting the total concentration of organic acids at 35, 40, 45, 50 %, it was seen that the strength and the coagulation time in the case of 35 % are inferior to those in the case of 40 %, the composition percentage in the case of 50 % is inferior to that in the case of 45 %, and that all said three capacities are superior in the area of 40~ 48 %.

As a result of the forementioned, as seen respectively in Fig. 1 and Fig. 2, said means for resolution in the very limited range was attained.

The hardening materials relating to the inventions in claims 9, 10, 13, and 14, by setting as above the proportion for combination of water and an organic acid (or water, an organic acid, and tannic acid) and by setting the kinds of organic acids and the proportion for combined use of an organic acid and tannic acid as described above, are able to compensate one another the physical properties which are inferior in the case of only one use of each organic acid. As a result, the strength of hardened products has become high, the decomposition percentage of hardened products has become low, and further the coagulation time has become properly slow. In addition, in a case that tannic acid is used, slow release of tannic acid, which has a pain-killing effect, from a hardened product is possible.

The hardening materials relating to the inventions in claims 9, 10, 13, and 14 are able to replace a 5 % at maximum or less of a total amount of the organic acids with an organic acid besides said four kinds of organic acids which is an organic acid shown in table 1 or an organic acid not shown in table 1, or may be with a salt derived from those acids as a component of a very small amount in a degree which does not damage the effects of this invention.

Also, an inorganic acid such as pyrophosphoric acid which participates in reaction with a small amount, a salt of an inorganic acid, and a polymer material such as acrylic acid, polyacrylic acid, and alginic acid can be added till 1 % of the solution in a case that an organic acid with water is mixed. Also, even if not directly participate in reaction, a protein substance such as collagen and collagen derivatives, a vitamin, and a polysuccaride, in a degree that a bad effect on physical properties is not given, can be added till 2 % of the solution in a case that an organic acid with water is mixed.

In each invention of claims 9, 10, 13, and 14, the combination proportion of calcium phosphate to a setting solution, which is prepared by dissolving an organic acid in water, is preferred to adjust the ratio by weight of calcium phosphate to a setting solution (g/ml) (so-called ratio of powder to liquid) at a range of 1.0~ 3.3. If deviates from this range, there sometimes occurs a problem that the coagulation and hardening does not take place or the mixing and kneading and the sealing operation become difficult.

Futhermore, according to the inventions in claims 9, 10, 13, and 14, even if the ratio of powder to liquid is varied in a considerably wide range, an advantage by which said (1) ~ (3) capacities does not widely vary can be obtained. Especially, in a three components system containing tannic acid and in a practically useful range of powder to liquid (the ratio of powder to liquid is 1.5 ~2.7), said three capacities are more stable than those in a two components system. In a case that a hardening material is usually used, because the powder is measured by a spoon without precise weighing and the liquid by drop number, the ratio of powder to liquid is often and considerably scattered, the forementioned is a significant advantage. Also, since a three components system containing tannic acid is a system in which tannic acid slowly releases, a pharmacological effect such as astriction of an inflammatory trouble in the oropharynx muscous membrance can be expected.

For the hardening materials relating to the present invention, as mentioned above, a main material is calcium powder in which at least either one component of 4CP and α-TCP is an essential component and any of the undermentioned (a)~ (f) is used as a hardening adjuster, so that the hardening proceeds at room temperature or around living body temperature and the hardening time can be elongated with almost absence of decrease in the operation efficiency for mixing and kneading and also, a character injurious for a body is absent.

(a) At least one compound from among tannin and tannin derivatives.

(b) At least one compound from among tannin and tannin derivatives and at least one compound from among collagen and collagen derivatives.

(c) At least one compound from among collagen and collagen derivatives and one or more of organic acids.

(d) At least one compound from among tannin and tannin derivatives, at least one compound from among collagen and collagen derivatives, and one or more of organic acids.

(e) At least one compound from among tannin and tannin derivatives and one or more of organic acids.

(f) Two or more of organic acids.

Therefore, the hardening materials relating to the present invention can be utilized for an use wherein the hardening needs a long time, and for an use wherein a hardened product of strong strength is needed by raising the ratio of calcium phosphate powder to a setting agent.

Since the hardening materials relating to the inventions in claims 9, 10, 13, and 14 are the ones wherein a hardening adjuster of specially-defined composition is used as mentioned above, they have almost no character injurious for a body, form a hardened product similar to the hard tissue of a living body, and have special properties to combine with the hard tissue of a living body and, therefore, the strength, decomposition percentage, and coagulating time of the hardened product are of practical use.

The hardening materials in this invention are not limited with the ones which contain only the essential components mentioned above, and the other materials may be combined in an extent which does not disturb resolution of the subjects in this invention. Also, among the hardening materials in this invention, said (i) ~ (iv) hardening materials may be, in addition to the above, combined with the other components in an extent which does not affect badly upon said (A) ~ (C) capacities. Here, the other materials means, for example, water, calcium phosphate other than α-TCP (4CP, HAp, and OCP etc.), X-ray contrast agents ($BaSO_4$ and bismuth salts etc.), pigments (TiO_2 etc.), coloring materials (β-carotine etc.), other kinds of inorganic oxides and inorganic salts (MgO, $MgCO_3$, and Al_2O_3 etc.), calcium gelation agents (jellan gum and chitosan etc.), coaking agents (polyalkyleneglycol and polyvinyl alcohol etc.), inorganic acids (pyrophosphonic acid, orthophosphonic acid, polyphosphonic acid, and hydrochloric acid etc.), polymolecular materials (acrylic acid and polyacrylic acid etc.), organic acid salts (sodium citrate and calcium citrate etc.). These are employed by alone or by combined two or more kinds.

[Brief Description of the Drawings]

Fig. 1 is triangular coordinates representing proportion for use of organic acids which are hardening materials relating to the inventions in claims 9 and 13. Fig. 2 is trianglular coordinates representing proportion for use of organic acids which are hardening materials relating to the inventions in claims 10 and 11. Fig. 3 is triangular coordinates representing proportion for use of organic acids wherein Fig. (a) shows resisting force for crushing, Fig. (b) decompositon percentage, and Fig. (c) coagulation time. Fig. 4 is triangular coordinates representing proportion for use of three kinds of organic acids which were prepared on a basis of the data in table 2.

Fig. 5 shows proportion for use in a case that two kinds of organic acids were used in combination wherein Fig. (a) is for resisting force for crushing, Fig. (b) for decomposition percentage, and Fig. (c) for coagulating time. Fig. 6 is a graph showing a relationship between the proportion for use, when two kinds of

organic acids are used in combination, and the coagulating time. Fig. 7 shows the concentration when an organic acid is used by alone, and Fig. (a) shows resisting force for crushing, Fig. (b) decomposition percentage, and Fig. (c) coagulating time. Each of Figs. from 8 to 12 is a graphs representing variation of capacities against the ratio of powder to liquid in the respective example, and each Fig. (a) shows variation of resisting force for crushing, each Fig. (b) variation of decomposition percentage, and each Fig. (c) variation of coagulation time.

[Best Mode for Carrying Out the Invention]

Hereinafter, the examples in this invention are presented with the examples for comparison, but this invention is not limited within said examples.

Examples 1 ~ 31 and examples for comparison 1 ~ 4

Solutions containing tannic acid, collagen, and organic acids in the concentration shown in table 3 and 4 are prepared, and the solutions were mixed with calcium phosphate powder, which shows the combination shown in tables 3 and 4, in a ratio of powder to liquid shown in tables 3 and 4 and then, they were kneaded by hand for about one minute. The undermentioned measurements were carried out by using the kneaded mud and the results obtained are shown in tables 3 and 4. The powder having an average particle diameter of 7 μm was used and aterocollagen (Cellmatrix LA produced from Nitta gelatin Inc.) was used as collagen. Besides, in the undermentioned measurements, all were carried out according to ADAS No. 61 under conditions of that the temperature was 23 ± 2 °C relative humidity 50 ± 10 %. However, for the examples 1, 2, 14, and 19, the measurements according to ADAS No. 57 were carried out.

(a) Measurements of time for hardening at an initial stage

Each the kneaded mud was poured into a metal mold of a cylinder shape made of stainless steel, which has an inner diameter of 10 mm and a height of 5 mm, and which is placed on a glass plate wherein a length, a width, and a thickness are all 15 mm, and the surface was made even and, at one minute after the kneading finished, the mud was transferred into a high temperature vessel showing temperature of 37 ± 1 °C and humidity of 100 % to prepare a piece for examination. The time, when a bikkar needle having a weight of 2.94 N (300 g) and a section area of 1 mm^2 is dropped on a surface of the piece for examination and a needle trace is not left, was assigned as the hardening time at an initial stage, calculating from the beginning of kneading. The hardening time at an initial stage was shown by taking an average of the values, obtained from three times measurements, by a 15 second unit.

(b) Measurements of resisting force for crushing

Each the kneaded mud was filled in a metal mold of a cylinder shape made of stainless steel, which has an inner diameter of 6 mm and a height of 12 mm, and its both ends were pinched with thick glass plates and then, it was pressurized. At 2.5 minutes since the kneading was initiated, the mud was transferred, maintaining the pressurizing, into a thermostat which was kept at temperature of 37 ± 1 °C and relative humidity of 100 %. After one hour the hardened product was taken out from the metal mold, immersed into distilled water of 37 ± 1 °C, and taken out from the distilled water at the time passage of 24 hours, since the kneading was initiated, to use it as a piece for examination. This piece for examination was subjected to mesurements of resisting force for crushing with an use of a Shimazu Autograph AG-2000 A. At the cross-head speed of 1 mm per minute, the measurements were carried out with six pieces for examination and the value measured was obtained by averaging the numeral values which remained after removal of the values showing - 15 % or less of the total avarage value. But, when there exist two or more of the values showing - 15 % or less of the total average value, the measurements were carried out again.

Table 3 (part 1 in two parts)

Combination of hardening materials for medical and dental use			example 1	example 2	example 3	example 4	example 5	example 6	example 7	example 8	example 9	example 10
	Calcium phosphate powder (weight %)	4CP	100	100	100	100	100	100	100	80	80	80
		α-TCP	—	—	—	—	—	—	—	20	—	10
		HAp	—	—	—	—	—	—	—	—	20	10
	Solution composition (weight %)	tannic acid	50	10	3	3	—	—	3	3	—	3
		collagen	—	1	—	—	0.5	0.5	0.5	—	0.5	0.5
		malic acid	—	—	40	40	40	40	40	40	40	40
		citric acid	—	—	10	—	10	—	10	10	10	10
		malonic acid	—	—	—	10	—	10	—	—	—	—
	Ratio between powder and liquid (g/ml)		1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Time for hardening at initial satage			10 hr. or more	24 hr. or more	6 min.	6 min.	6 min.	6 min.	8 min.	7.5 min.	7.5 min.	7 min.
Resisting force for crushing of hardened product at initial stage (kgf/cm^2)			—	—	920	920	950	950	1400	1100	950	1000

(Note) The residual part of solution is water.

The time for hardening for examples 1, 2, and 14 was determined according to ADA Specification No. 57.

The others were determined according to ADA Specification No. 61.

Table 3 (part 2 in two parts)

Combination of hardening materials for medical and dental use			example 11	example 12	example 13	example 14	example 15	example 16	example 17	example 18	example for comparison 1	example for comparison 2
	Calcium phosphate powder (weight %)	4CP	20	100	80	80	100	100	80	80	80	80
		α-TCP	80	—	—	20	—	—	20	—	20	20
		HAp	—	—	20	—	—	—	—	20	—	—
	Solution composition (weight %)	tannic acid	3	3	—	50	—	—	—	—	—	—
		collagen	—	—	0.5	—	—	—	—	—	—	—
		malic acid	40	40	40	—	40	40	40	40	50	40
		citric acid	10	10	10	—	10	10	10	10	—	—
		malonic acid	—	—	—	—	—	—	—	—	—	—
	Ratio between powder and liquid (g/ml)		1.5	2.0	2.0	1.5	1.5	2.0	1.5	2.0	1.5	1.5
Time for hardening at initial satage			7 min.	5 min.	4.75 min.	10 hr or more	4.5 min.	3 min.	3.5 min.	2.25 min.	3.5 min.	3.0 min.
Resisting force for crushing of hardened product at initial stage (kgf/cm^2)			1200	1100	1100	—	900	950	900	950	850	900

(Note) The residual part of solution is water.

The time for hardening for examples 1, 2, and 14 was determined according to ADA Specification No. 57.

The others were determined according to ADA Specification No. 61.

Table 4 (part 1 in two parts)

Combination of hardening materials for medical and dental use			example 19	example 20	example 21	example 22	example 23	example 24	example 25	example 26
Calcium phosphate powder (weight %)	4CP		—	—	—	—	—	—	—	—
	α-TCP		100	100	100	100	80	80	80	100
	HAp		—	—	—	—	20	20	20	—
Solution composition (weight %)	tannic acid		10	3	—	3	3	—	3	3
	collagen		1	—	0.5	0.5	—	0.5	0.5	—
	malic acid		—	—	—	—	—	—	—	—
	citric acid		—	45	45	45	45	45	45	45
	malonic acid		—	7	7	7	7	7	7	7
Ratio between powder and liquid (g/ml)			2.0	2.0	2.0	2.0	2.0	2.0	2.0	3.0
Time for hardening at initial satage			24 hr. or more	6 min.	6 min.	8 min.	5.5 min.	5.75 min.	7.5 min.	5.5 min.
Resisting force for crushing of hardened product at initial stage (kgf/cm^2)			—	1120	1400	1500	1100	1350	1450	1700

(Note) The residual part of solution is water.

The time for hardening for example 19 was determined according to ADA Specification No. 57.

The others were determined according to ADA Specification No. 61.

Table 4 (part 2 in two parts)

Combination of hardening materials for medical and dental use			example 27	example 28	example 29	example 30	example 31	example for comparison 3	example for comparison 4
	Calcium phosphate powder (weight %)	4CP	—	—	—	—	—	—	—
		α-TCP	80	100	100	80	80	100	100
		HAp	20	—	—	20	20	—	—
	Solution composition (weight %)	tannic acid	—	—	—	—	—	—	—
		collagen	0.5	—	—	—	—	—	—
		malic acid	—	—	—	—	—	—	—
		citric acid	45	45	45	45	45	52	45
		malonic acid	7	7	7	7	7	—	—
	Ratio between powder and liquid (g/ml)		3.0	2.0	3.0	2.0	3.0	2.0	2.0
Time for hardening at initial satage			5.5 min.	4.5 min.	3 min.	4 min.	2.5 min.	4.5 min.	3.5 min.
Resisting force for crushing of hardened product at initial stage (kgf/cm^2)			1700	1100	1300	1000	1250	1050	1000

(Note) The residual part of solution is water.
The time for hardening for example 19 was determined according to ADA Specification No. 57.
The others were determined according to ADA Specification No. 61.

As seen in tables 3 and 4, the materials in the examples 1, 2 14, and 19 proceeded with a hardening process at the initial stage slower than a case of that an organic acid was used as a hardening adjuster, so that they better fits for sealing a root canal. Compared the examples 3~ 13 and 15 ~ 18 with the examples for comparison 1 and 2 and also, the examples 20 ~ 31 with the examples for comparison 3 and 4, the examples showed longer hardening time at the initial stage. In addition, since a setting solution containing one or more kinds of organic acids is used for the examples for comparison 1~ 4, in order to delay the hardening time the concentration may be enhanced or the ratio between powder and liquid may be lower. However, if the concentration of the setting solution was enhanced, greater force was required for kneading, and if the ratio between powder and liquid was lowered, the resisting force for crushing at an initial stage tended to lower. Even though, as shown in the examples 12, 13, 26, and 27, the ratio between powder and liquid was enhanced and the resisting force for crushing of the hardened product was enhanced, the hardening time at an initial stage was such long as in an extent that was practically no problem. However, in

the examples 16, 18, 29, and 31, with enhancement of the ratio between powder and liquid the hardening time at an initial stage became extremely short. Also, in the cases that collagen was used (examples 5 ~ 7, 9, 10, 13, 21, 22, 24, 25, and 27), the resisting force for crushing at an initial stage clearly increased and, in particular, the case that tannin was used in combination showed specially enhanced performance.

When each of the materials in the examples 3 ~ 13, 15 ~ 18, and 20 ~ 31, and the examples for comparison 1~ 4 was immersed in PBS, the cases of that collagen was used showed that, even after the hardening at the initial stage, the resisting force for crushing was increasing with time-passage.

Besides, each material in the examples 3 ~ 13, 15 ~ 18, and 20 ~ 31 was hardened at an initial stage to a piece of a cylindrical shape of ϕ 6 mm x length 12 mm, buried in a defective part of femur of a dog, taken out after standing, respectively, for 2, 4, and 6 weeks, and evaluated by tissue observation at a surface conjugated with a bone tissure and by a pushing-out method which is to see conjugation force with the bone. As a result, in the cases of materials in the examples 15~ 18 and 28 ~ 31, although a direct conjugation with a bone was initiated, a slight degree of cell inflitration of a circular shape was observed. Also, in each material of the examples 3~ 13 and 20 ~ 27, no inflammatory reaction of such a kind was found and a direct conjugation with a bone already progressed. When the materials of the examples 15~ 18 and 28 ~ 31 were stood for 4 and 6 weeks after transplantation, the inflammatory symtoms gradually disappear and gradually increasing bond-formation in this part was observed. In each material of the examples 3 ~ 13 and 20 ~ 27, there existed bone cells in an interface with the bone tissue. Especially, in the cases of that collagen was used (examples 5~ 7, 9, 10, 13, 21, 22, 24, 25, and 27), a number of bone cells existed in the circumference of the interface and the rigidly conjugating force with a bone increased by leaps and bounds.

Example 32

Prepared was a hardening material composed of a powder agent, which was composed of 80 % of 4CP and 20 % of α-TCP, and a setting solution (a liquid agent) which was made by dissolving into water a composition composed of 40 % of malic acid, 10 % of citric acid, and 5 % of gluconic acid. In this example the malic acid, citric acid, and gluconic acid are hardening adjusters.

Example 33

Prepared was a hardening material composed of a powder agent, which was composed of 80 % of 4CP and 20 % of α-TCP, and a setting solution (a liquid agent) which was made by dissolving into water a composition composed of 40 % of malic acid, 10 % of citric acid, and 5 % of lactic acid. In this example the malic acid, citric acid, and lactic acid are hardening agents.

Example 34

Prepared was a hardening material composed of a powder agent, which was composed of 80 % of 4CP and 20 % of α-TCP, and a setting solution (a liquid agent) which was made by dissolving into water malic acid, citric acid, and acid-soluble collagen (Cellmatrix type I -A produced from Nitta Gelatin Inc., which converts into fibrils within 8 minutes under physiological conditions) in their respective proportions of 40, 10, and 0.5 %. In this example the malic acid, citric acid, and collagen are hardening adjusters.

Example 35

Prepared was a hardening material composed of a powder agent, which was composed of 80 % of 4CP and 20 % of α-TCP, and a setting solution (a liquid agent) which was made by dissolving into water malic acid, citric acid, the type II collagen (Cellmatrix type II produced from Nitta Gelatin Inc., which does not convert into fibrils under physiological conditions), and decomposed gelatin (water-soluble gelatin produced from Nitta Gelatin Inc., which does not convert into fibrils under physiological conditions) in their respective proportions of 40, 10, 0.5, and 1 %. In this example the malic acid, citric acid, type II collagen, and decomposed gelatin are hardening adjusters.

Example 36

Prepared was a hardening material composed of a powder agent, which was composed of 78 % of 4CP, 20 % of α -TCP, and 2 % of zinc tannate, and a setting solution (a liquid agent) which was made by

dissolving into water malic acid and citric acid in their respective proportions of 40 and 10 %. In this example the malic acid, citric acid, and zinc tannate are hardening adjusters.

Example 37

Prepared was a hardening material composed of a powder agent, which was composed of 75 % of 4CP, 20 % of α-TCP, and 5 % of albumin tannate, and a setting solution (a liquid agent) which was made by dissolving into water malic acid and citric acid in their respective proportions of 40 and 10 %. In this example the malic acid, citric acid, and albumin tannate are hardening adjusters.

Example 38

Prepared was a hardening material composed of a powder agent, which was composed of 34.6 % of α-TCP, 20.4 % of 4CP, 28.0 % of HAp, 2 % of TiO_2, 10 % of $BaSO_4$, 0.5 % of β-carotene, 2 % of bismuth pyrogallate, 0.5 % of MgO, and 2 % of calcium citrate, and a setting solution (a liquid agent) which was made by dissolving into water citric acid, malonic acid, malic acid, gluconic acid, chitosan, carboxymethyl-chitin, jellan gum, polyalkyleneglycol, polyphosphoric acid, tannic acid, aterocollagen (Cellmatrix produced from Nitta Gelatin Inc., which converts into fibrils with a time longer than 8 minutes under physiological conditions), glycolic acid, pyruvic acid, and phytic acid in their respective proportions of 1.0, 2.0, 2.0, 2.0, 1.0, 1.0, 1.0, 1.0, 0.5, 15, 2, 0.5, 0.5, and 0.5 %. In this example the bismuth pyrogallte, citric acid, malonic acid, malic acid, gluconic acid, tannic acid, aterocollagen, glycolic acid, pyruvic acid, and phytic acid are hardening adjusters.

Each hardening material in the examples 32 ~ 38 was mixed in the ratio of powder to liquid shown in table 5 and kneaded as carried out in the example 1 and then, the time for hardening at the initial stage and the resisting force for crushing were examined as carried out in the example 1. Results are presented in table 5.

Table 5

	powder/liquid ratio (g/ml)	time for hardening at initial stage	resisting force for crushing of hardened product at initial stage (kgf/cm²)
example 32	1.5	8.0 min.	900
example 33	1.5	5.0 min.	900
example 34	1.5	4.5 min.	1000
example 35	1.5	5.0 min.	900
example 36	1.5	6.0 min.	1000
example 37	1.5	4.5 min.	900
example 38	1.5	12.0 min.	110

The capacities does not decrease and, as shown in table 5, the time for hardening at the initial stage was adjusted (refer to the examples for comparison 1 and 2 in table 3 and the example 17).

Hereinafter, concrete examples and examples for comparison for the hardening materials relating to the inventions in claim 9, 10, 13, and 14 are shown, but the inventions are not limited within the below-described examples.

The powder used had an averaged particle diameter in a range of 1 ~ 20 μm.

Examples 39 ~ 48 and examples for comparison 5 and 6

The hardening materials were prepared with the combination shown in table 6.

Examples 49 ~ 54 and examples for comparison 7 and 8

The hardening materials were prepared with the combination shown in table 7.

For the hardening materials in said examples and examples for comparison the powder and the liquid were mixed and kneaded under room temperature and the resisting force for crushing, decomposition percentage, and coagulating time were determined according to JIS T6602. Results are shown in tables 6 and 7 together with the combination ratio in the hardening materials.

Table 6

			example 39	example 40	example 41	example 42	example 43	example 44	example 45	example 46	example 47	example 48	example for comparison 5	example for comparison 6
combination of hardening materials	powder agent (%)	α-TCP	100	100	100	100	100	100	100	80	80	63	100	63
		4CP	—	—	—	—	—	—	—	20	20	37	—	37
	total concentration of organic acids in setting solution(%)		45	45	45	45	45	45	45	47	47	45	45	45
	proportion for use of organic acids *1 (parts)	citric acid	65	85	85	60	70	75	89	70	89	65	55	40
		malonic acid	35	15	—	30	20	—	—	—	—	20	45	10
		tannic acid	—	—	15	10	10	25	11	30	11	15	—	50
	powder/liquid ratio (g/ml)		2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.6	2.6	2.3	2.5	2.3
resisting force for crushing (kgf/cm^2)			1350	1500	1500	1500	1600	1250	1400	1250	1500	1350	1600	450
decomposition percentage(%)			2.0	1.7	1.6	1.6	1.7	1.7	2.0	1.6	1.8	1.8	4.5	5.0
coagulating time (min.)			4.5	3.5	4.5	4.5	4.0	6.0	7.0	4.5	5.0	5.0	6.0	50

*1 proportion against 100 parts of total organic acids (part)

Table 7

combination of hardening materials		example 49	example 50	example 51	example 52	example 53	example for comparison 7	example for comparison 8	example 54	example for comparison 9
powder agent (%)	α-TCP	100	100	100	100	100	100	100	63	63
	4CP	—	—	—	—	—	—	—	37	37
total concentration of organic acids in setting solution(%)		45	45	45	45	45	45	45	45	45
proportion for use of organic acids *1 (parts)	citric acid	65	10	—	65	30	75	—	65	10
	malic acid	35	90	90	20	60	25	75	20	40
	tannic acid	—	—	10	15	10	—	25	15	50
powder/liquid ratio (g/ml)		2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.3	2.3
resisting force for crushing (kgf/cm^2)		1550	1450	1400	1550	1550	1550	1250	1350	400
decomposition percentage(%)		2.0	2.0	2.0	1.8	1.8	2.5	2.5	1.8	5.5
coagulating time (min.)		3.0	5.0	6.0	4.0	6.0	1.8	8.5	4.0	6.0

*1 proportion against 100 parts of total organic acids (part)

As seen in tables 6 and 7, the hardening materials in the examples made hardened products of high resisting force for crushing and low decomposition percentage, and their coagulating time was properly slow.

In the examples for comparison, sometimes the resisting force for crushing was small, the decomposition percentage was large, and the coagulating time was too short or too long.

Example 55

Prepared was a hardening material composed of a setting solution, which was prepared by dissolving into water citric acid and malonic acid in their respective proportions of 39 and 6 %, and α-TCP.

Example 56

Prepared was a hardening material composed of a setting solution, which was prepared by dissolving into water malic acid and citric acid in their respective proportions of 36 and 9 %, and α-TCP.

Example 57

Prepared was a hardening material composed of a setting solution, which was prepared by dissloving into water citric acid, malonic acid, and tannic acid in their respective proportions of 35, 5, and 5 %, and α-TCP.

Example 58

Prepared was a hardening material composed of a setting solution, which was prepared by dissolving into water malic acid, citric acid, and tannic acid in their respective proportions of 32, 8, and 5 %, and α-TCP.

Example 59

Prepared was a hardening material composed of a powder agent, which was composed of 47.2 % of α-TCP, 27.8 % of 4CP, 7 % of HAp, 2 % of TiO_2, 10 % of $BaSO_4$, 1 % of CaF_2, 0.5 % of β-carotene, 2 % of bismuth pyrogallate, 0.5 % of MgO, and 2 % of calcium citrate, and a setting solution (a liquid agent) which was prepared by dissolving into water citric acid, malonic acid, malic acid, gluconic acid, chitosan, jellan gum, polyalkyleneglyco 1, polyphosphoric acid, tannic acid, aterocollagen (Cellmatrix LA produced from Nitta Gelatin Inc., which converts into fibrils with a time longer than 8 minutes under physiological conditions), glycolic acid, pyruvic acid, and phytic acid in their respective proportions of 32. 1, 5.4, 1.3, 0.1, 0.5, 0.5, 0.5, 0.5, 4.5, 0.5, 0.5, 0.1, and 0.5 %. In this example the bismuth pyrogallate, citric acid, malonic acid, malic acid, gluconic acid, tannic acid, aterocollagen, glycolic acid, pyruvic acid, and phytic acid are hardening adjusters.

Example 60

Prepared was a hardening material composed of a powder agent, which was composed of 47.2 % of α-TCP, 27.8 % of 4CP, 7 % of HAp, 2 % of TiO_2, 10 % of $BaSO_4$, 1 % of CaF_2, 0.5 % of β-carotene, 2 % of bismuth pyrogallate, 0.5 % of MgO, and 2 % of calcium citrate, and a setting solution (a liquid agent) which was prepared by dissolving into water citric acid, malic acid, gluconic acid, chitosan, jellan gum, polyalkyleneglycol, polyphosphoric acid, aterocollagen (Cellmatrix LA, produced from Nitta Gelatin Inc.; which converts into fibrils taking a longer time than 8 minutes under a physiological condition.), glycolic acid,pyruvic acid, and phytic acid in their respective proportions of 42 %, 1.3 %, 0.1 %, 0.5 %, 0.5 %, 0.5 %, 0.5 %, 0.5 %, 0.5 %, 0.1 %, and 0.5 %. In this example, bismuth pyrogallate, citric acid, malic acid, gluconic acid, aterocollagen, glycolic acid, pyruvic acid, and phytic acid are hardening adjusters.

Example 61

Prepared was a hardening material composed of a powder agent, which is composed of 47.2 % of α-TCP, 27.8 % of 4CP, 7 % of HAp, 2 % of TiO_2, 10 % of $BaSO_4$, 1 % of CaF_2, 0.5 % of β-carotene, 2 % of bismuth pyrogallate, 0.5 % of MgO, and 2 % of calcium citrate, and a setting solution (a liquid agent) which was prepared by dissolving into water citric acid, malic acid, gluconic acid, chitosan, jellan gum, polyalkyleneglycol, polyphosphoric acid, aterocollagen (Cellmatrix LA, produced from Nitta Gelatin Inc., which converts into fibrils taking a longer time than 8 minutes under a physiological condition.), glycolic acid, pyruvic acid, and phytic acid in their respective proportions of 32.1 %, 1.3 %, 0.1 % 0.5 %, 0.5 %, 0.5 %, 0.5 %, 0.5 %, 0.5 %, 0.1 %, and 0.5 %. In this example, bismuth pyrogallate, citric acid, malic acid, gluconic acid, aterocollagen, glycolic acid, pyruvic acid, and phytic acid are hardening adjusters.

Variation of the resisting force for crushing, the decomposition percentage, and the coagulating time were investigated when the powder to liquid ratio of each hardening material in the example 55~ 61 was changed. For comparison, taking 45 %, 39 %, and 35 % aqueous solutions of citric acid (regarding the examples 55 and 57) and 45 %, 36 %, and 32 % aqueous solutions of malic acid (regarding the examples 56 and 58) as setting solutions, and with changing the powder to liquid ratio in the hardening materials composed of said setting solutions and α-TCP, variation of the resisting force for crushing, the decomposition percentage, and the coagulating time were investigated. Results were showed in Figures 8 (example 55), 9 (example 56), 10 (example 57), 11 (example 58), and 12 (example 59~ 61), respectively. In Figures 8~ 12, the figures (a) show variation of the resisting force for crushing (kg f / cm^2), the figures (b) that of the decompositon percentage (%), and the figures (c) that of the coagulating time (min.). In Figures 8 ~ 11, a curved line connecting the black circles is for the examples and curved lines connecting the opened circles and the triangles are, respectively, for examples in which an aqueous solution of only citrc acid or an aqueous solution of only malic acid is the setting solution. Also, in Figure 12, a curved line connecting the black circles is for example 59, a curved line connecting the opened circles for example 60, and a curved line connecting the triangles for example 61.

As seen in Figures 8 ~ 11, respectively, the hardening materials in the inventions as claimed in claims 9, 10, 13, and 14 show relatively small variation of capacities with the changing powder to liquid ratio. Also, as seen in Figure 12, when a case of that citric acid, malonic acid, and tannic acid are defined in said special combination proportion (example 59) is compared with a case of that deviates from the defined combination proportion, the resisting force for crushing varied to a higher direction, the decompositon percentage to a smaller direction, and the coagulating time to a longer direction. That is, it is seen that, even if another component is added to said defined combination proportion, the good physical properties are still displayed.

Examples in the case of that the hardening materials in the present invention are used for a root canal sealer are shown hereinafter with examples for comparison.

Example 62

Prepared was a hardening material composed of a powder agent of 100 % of α-TCP and a setting solution (a liquid agent) which was prepared by dissolving into water citric acid and tannic acid in their respective proportions of 22.5 % and 22.5 %.

Example 63

Prepared was a hardening material composed of a powder agent of 100 % of α-TCP and a setting solution (a liquid agent) which was prepared by dissolving into water citric acid and tannic acid in their respective proportions of 13 % and 32 %.

Example 64

Prepared was a hardening material composed of a powder agent of 100 % of 4CP and a setting solution (a setting solution) which was prepared by dissolving into water citric acid and tannic acid in their respective proportions of 8 % and 22 %.

Example 65

Prepared was a hardening material composed of a powder agent, which was composed of 63 % of α-TCP and 37 % of 4CP, and a setting solution (a setting liquid) which was prepared by dissolving into water citric acid and tannic acid in their respective proportions of 2 % and 5 %.

Example 66

Prepared was a hardening material composed of a powder agent, which was composed of 44 % of α-TCP, 26 % of 4CP, 10 % of bismuth pyrogallate, and 20 % of $BaSO_4$, and a setting solution (a liquid agent) which was prepared by dissolving into water citric acid and tannic acid in their respective proportions of 2 % and 5 %.

Example 67

Prepared was a hardening material composed of a powder agent, which was composed of 98 % of 4CP and 2 % of carboxymethylchitin, and a setting solution (a liquid agent) which was prepared by dissolving into water aterocollagen (Cellmatrix LA, produced from Nitta Gelatin Inc.), malic acid, and citric acid in their proportions of 0.5 %, 18 %, and 4.5 %.

Example 68

Prepared was a hardening material composed of a powder agent of 100 % of 4CP and a setting solution (a liquid agent) which was prepared by dissloving into water alginic acid, malic acid, and citric acid into their respective proportions of 0.5 %, 18 %, and 4.5 %.

Example 69

Prepared was a hardening material composed of a powder agent, which was composed of 95 % of 4CP and 5 % of aterocollagen (Cellmatrix LA, produced from Nitta Gelatin Inc.), and a setting solution (a liquid agent) which was prepared by dissolving into water aluginic acid, malic acid, and citric acid in their repective proportions of 0.5 %, 18 %, and 4.5 %.

Example 70

Prepared was a hardening material composed of a powder agent of 100 % of 4CP and a setting solution (a liquid agent) which was prepared by dissolving into water xanthan gum, malic acid, and citric acid in their proportions of 0.3 %, 15 %, and 3.7 %.

Example 71

Prepared was a hardening material composed of a powder agent of 100 % of 4CP and a setting solution (a liquid agent) which was prepared by dissolving into water aterocollagen (Cellmatrix LA, produced from Nitta Gelatin Inc.), xanthan gum, malic acid, and citric acid in their respective proportions of 0.3 %, 0.3 %, 15 %, and 3.7 %.

Example for comparison 10

Prepared was a root canal sealer composed of a powder agent, which was composed of 20 % of 4CP, 20 % of MgO, 20 % of rosin, and 40 % of bismuth bicarbonate, and a solvent composed of 100 % of oleic acid.

Example for comparison 11

Prepared was a root canal sealer composed of a powder agent, which was composed of 43 % of 4CP, 20 % of MgO, 30 % of bismuth bicarbonate, and 0.7 % of $Ca(OH)_2$, and a solvent composed of 100 % of euginol.

Example for comparison 12

Used was a root canal sealer commercially available from Showa Yakuhin Kagaku Kogyo Co., Ltd. (Kyanarusu of a trade name).

For the materials in the examples 62 ~ 71 and the examples for comparison 10 ~ 12, according to the ISO standards (International Organization for Standardization) 6876-1986 (E), the flow (a degree of flowing with press), time for hardening, solubility, degree of decomposition (referred to as 「 decomposition percentage 」), and resisting force for crushing were determined. Besides, using an aqueous solution in which the decomposition percentage was already determined, tannic acid eluded was confirmed with a colorimeter. Furthermore, cement or a root canal sealer was filled with pressure for a place where a molar dental pulp of a grown dog was extracted and then, stood for 3 months. Tooth extraction was followed by setting and then, a slice for polishing which did not decalcificate was subjected to a pathological observation with haematoxyline-eosine (referred to as 「 H • E 」) coloring.

1) Flow (degree of flowing with press);

A root canal sealer kneaded, 0.075 mℓ is placed on a glass plate and, at 3 minutes after the kneading is initiated, a load of 2.5 kg is imposed. Then, the flow is determined by a diameter of that the kneaded mud spread.

According to the ISO standards, the value is defined as 20 mm or more.

2) Time for hardening;

A kneaded mud is filled in a ring having a diameter of 10 mm and a height of 2 mm and the time that, at 2 minutes after the kneading is initiated, a Gilmore needle having a load of 100 g and a diameter of 2 mm does not give a pressed trace under the conditions of ordinary temperature of 37 °C and relative humidity of 95 % or more, is defined as the time for hardening.

3) Solubility and decomposition degree (decomposition percentage);

A kneaded mud is filled in a ring having a diameter of 20 mm and a thickness of about 1.5 mm and, under the conditions of room temperature of 37 °C and relative humidity of 95 % or more, stood for hardening for a time that is 1.5 times of a time for hardening of each cement, whereby a slice for examination is obtained. This slice is immersed in 50 mℓ of distilled water at 37 °C for 24 hours and then, the water in a stoppered bottle is evaporated at 150 °C until dryness, whereby the solubility is determined from the weight of the sample before immersing and the residue amount in the stoppered bottle.

The standard for this is 2 w / w % or less.

Besides, since it is considered that, in this experiment, the decomposing character into water is a unfavarable phenomenon, the decompositon percentage is determined as including the solubility and the decomposition amount.

4) Resisting force for crushing

A slice having a diameter of 6 mm and a height of 12 mm is prepared and stood for 24 hours under the conditions of room temperature of 37 °C and relative humidity of 100 % and then, the resisting force for crushing is determined.

The determination is carried out with a Shimazu 0-graph IS-5000 and with a cross-head speed of 0.5 mm per minute.

5) Slow-release of tannic acid from hardened product

A slice prepared in a similar way as used for determination of the decomposition degree is immersed in 50 ml of distilled water at 37 °C for 24 hours and then, the water in a stoppered bottle is taken as a solution for examination. This solution for examination, 5 mℓ, is treated with addition of 2 drops of a test solution of ferric chloride and subjected to a quantitative measurement with a colorimeter at 590 nm, thereby presence or absence of tannic acid is confirmed.

6) Pathological observation with filling into a molar root canal of a grown dog

A molar dental pulp of a grown dog is extracted and then, without combination use of a point such as guttapercha point, each cement or kneaded mud of a root canal sealer is filled with pressure into a washed root canal and, the crown part is filled and restored with use of glass-ionomer cement. With passage of three months, a slice for polishing which was not decalicificated was prepared by tooth extraction followed by setting with a 10 % aqueous formaline solution. After the H • E coloring treatment, a pathological observation was carried out.

Results are shown in Table 8.

Table 8

	Powder to liquid ratio (g/ml)	Flow (mm)	Time for hardening	Decomposition percentage (w/w %)	Resisting force for crushing (kgf/cm²)	Slow-release of tannic acid	Remark on pathological sample
example 62	2.0	25	51 min.	1.21	230	presence	closing of apical hole with fibrous tissue
example 63	2.0	35	3 hr.	1.63	120	presence	closing of apical hole with fibrous tissue
example 64	2.0	38	8 hr.	1.83	105	presence	closing of apical hole with fibrous tissue and calcification of directly down part
example 65	2.0	36	12 hr.	0.95	110	presence	closing of apical hole with fibrous tissue and calcification of directly down part
example 66	2.0	28	48 hr.	1.53	100	presence	closing of apical hole with fibrous tissue and calcification of directly down part
example 67	2.0	39	12 hr.	0.33	160	absence	calcification of apical hole and closing of apical hole with growth of cement
example 68	2.0	31	40 min.	0.91	90	absence	closing of apical hole with fibrous tissue and calcification of directly down part
example 69	2.0	33	2 hr.	0.83	105	absence	calcification of root canal and closing of apical hole with growth of cement
example 70	2.0	30	45 min.	0.90	80	absence	closing of apical hole with fibrous tissue
example 71	2.0	27	3 hr.	0.72	100	absence	calcification of root canal and closing of apical hole with growth of cement
example for comparison 10	4.0	22	30 min.	0.49	—	absence	confirmation of local inflammatory megakaryocyte in apical hole
example for comparison 11	4.0	30	20 min.	0.71	—	absence	confirmation of pus blister in gum around apical hole
example for comparison 12	5.0	40	2 hr.	0.90	110	absence	confirmation of pus blister in gum around apical hole

As seen in Table 8, although there is no problem in the examples, inflammation and pus blister were confirmed in the examples for comparison.

Besides, concerning each of the hardening materials in the examples and the examples for comparison shown above as well as in the examples for comparison 13~ 15 described below, the powder and liquid were both treated with sterilization, mixed, and kneaded for about 1 minute, whereby the mud obtained was treated with an initial hardening during only the time for hardening of each hardening material to make a cylindrical piece having a diameter of 4 mm and a length of 10 mm. These pieces were inserted into the femoral bone shaft of a grown dog by making a drill hole which is just 0.2 ~ 0.3 mm larger than said pieces and each hardening material was buried for 2, 4, and 6 weeks. Then, for each hardening material the slices

for polishing which were decalcificated and not decalcificated were prepared. The slice decalcificated was colored with the H • E coloring and with toluidine blue to carry out a pathological observation, and the slice for polishing not decalicificated was colored With the H • E coloring to do that. Furthermore, concerning the force for fixing with a bone tissue, force for cutting was measured, according to a pushing-out method with 0.1 mm/min. of a cross-head speed, by using an universal test machine of a rod cell type. Results are shown in Table 9.

Example for comparison 13

Used was a hardening material composed of combination of a powder agent, which was composed of 100 % of α-TCP, with a setting solution (a liquid agent) composed of 40 % of polyacrylic acid.

Example for comparison 14

Used was a hardening material composed of combination of a powder agent, which was composed of 61 % of α-TCP, 36 % of 4CP, and 3 % of HAp, with a setting solution (a liquid agent) which was prepared by dissolving into water polyacrylic acid and citric acid in their respective proportion of 17 % and 30 %.

Example for comparison 15

Used was bone cement in a PMMA series commercially available from Howmedica Co., Ltd. (Surgical Simplex in the trade name).

Table 9

	Pathological remark	Fixing force with bone tissue
example 1	After 2 weeks, direct bond with a bone was in part observed, but slight cell wetness of a circle shape was found. After 4 and 6 weeks, inflammation symptoms gradually disappeared and at this part bone formation gradually increased in amount.	After 6 weeks: 30 kgf/cm^2
examples 5, 7, 10, 19, 21, 22, 25, and 35	Inflammation reaction was not observed. After 2 weeks, direct bond formation with a bone began. After 4 weeks, a number of bone cells existed around an interface with the bone tissue. After 6 weeks, the bone increased in amount.	After 6 weeks: 70 kgf/cm^2
examples 2 and 38	Almost no inflammatory reaction. After 4 weeks, direct bond formation with a bone had already begun and at an interface bone cells existed.	After 6 weeks: 45 kgf/cm^2
examples 12, 20, 40, 42, 45, 47, 48, 50, 51, 52, and 54	Almost no inflammatory reaction. After 4 weeks, direct bond formation with a bone had already begun and at an interface bone cells existed.	After 6 weeks: 30 kgf/cm^2
examples for comparison 2 and 4	Same to example 1	After 6 weeks: 20 kgf/cm^2
example for comparison 13	After 2 weeks, a connective tissue with a bone tissue existed. Inflammatory reaction and cell wetness were found. After 4 and 6 weeks, was the same.	After 6 weeks: 1 kgf/cm^2
example for comparison 14	After 2 weeks, a connective tissue with a bone tissue existed. Slight inflammatory reaction and cell wetness were found. After 6 weeks, although bond formation with a bone tissue was in part observed, the parts where connective tissue existed was major.	After 6 weeks: 5 kgf/cm^2
example for comparison 15	Almost no inflammatory reaction. A connective tissue with a bone tissue existed and there is no bond part with a bone.	After 6 weeks: 0.5 kgf/cm^2

As seen in Table 9, fixing force with a bone tissue in the examples was higher than that in the examples for comparison and, in particular, the examples in which aterocollagen was used was better.

(Industrial Applicability)

The hardening material relating to the present invention can be used as a root canal sealer, cement and a filling agent for dental use, bone cement and a filling agent, and the like.

Claims

1. A hardening material for medical and dental use, in which calcium phosphate powder containing at least either one of α-tricalcium phosphate and tetracalcium phosphate is an essential component, characterised in that at least two kinds of organic acids are used as a hardening adjuster.

2. A hardening material for medical and dental use as claimed in claim 1, in which the organic acid is selected from citric acid, malic acid, and malonic acid.

3. A hardening material for medical and dental use as claimed in claim 2, in which α-tricalcium phosphate, the organic acid, and water are essential components, wherein the proportions of said water and the organic acid are such that the organic acid comprises 40 - 48 % by weight and the residual part is water, said organic acid comprises citric acid and malonic acid, and the mutual proportions of citric acid and malonic acid are, against 100 parts by weight of the total of the two acids, 65 - 90 parts by weight for citric acid and 10 35 parts by weight for malonic acid.

4. A hardening material for medical and dental use as claimed in claim 2, in which α-tricalcium phosphate, the organic acid, and water are essential components, wherein the proportions of said water and the organic acid are such that the organic acid comprises 40 - 48 % by weight and the residual part is water, said organic acid comprises citric acid and malic acid, and the mutual proportions of citric acid and malic acid are, against 100 parts by weight of a total of these two acids, 10 - 65 parts by weight for citric acid and 35 - 90 parts by weight for malic acid.

5. A hardening material for medical and dental use, in which calcium phosphate powder containing at least either one of α-tricalcium phosphate and tetracalcium phosphate is an essential component, characterised in that at least either one compound of tannin and a tannin derivative and one or more kinds of organic acid are used as a hardening adjuster.

6. A hardening material for medical and dental use as claimed in claim 5, in which said either one compound of tannin and said tannin derivative is tannic acid and the organic acid is selected from citric acid, malic acid, and malonic acid.

7. A hardening material for medical and dental use as claimed in claim 6, in which α-tricalcium phosphate, the organic acid, and water are essential components, wherein the proportions of said water, organic acid, and tannic acid are such that the total amount of the organic acid and tannic acid comprises 40 - 48 % by weight and the residual part is water, said organic acid is at least one of citric acid and malonic acid, and the mutual proportions of citric acid, malonic acid, and tannic acid are, against 100 parts by weight of a total of the three acids, 60 - 90 parts by weight for citric acid, O - 35 parts by weight for malonic acid, and 30 parts or less by weight for tannic acid.

8. A hardening material for medical and dental use as claimed in Claim 7, wherein the proportion of malonic acid is 0 parts by weight, the proportion of citric acid is 70 - 89 parts by weight, and the proportion of tannic acid is 30 - 11 parts by weight.

9. A hardening material for medical and dental use as claimed in claim 6, in which α-tricalcium phosphate, the organic acid, and water are essential components, wherein the proportions of said water, organic acid, and tannic acid are such that the total amount of the organic acid and tannic acid comprises 40 - 48 % by weight and the residual part is water, said organic acid is at least one of citric acid and malic acid, and the mutual proportions of citric acid, malic acid, and tannic acid are, against 100 parts by weight of a total of the three acids, 0 - 65 parts by weight for citric acid, 20 - 90 parts by weight for malic acid, and 15 parts or less by weight for tannic acid.

10. A hardening material for medical and dental use, in which calcium phosphate powder containing at least either one of α-tricalcium phosphate and tetracalcium phosphate is an essential component, characterised in that at least either one compound of tannin and a tannin derivative is used as a hardening adjuster.

11. A hardening material for medical and dental use, in which calcium phosphate powder containing at least either one of α-tricalcium phosphate and tetracalcium phosphate is an essential component, characterised in that at least either one compound of tannin and a tannin derivative and at least either one compound of collagen and a collagen derivative are used as a hardening adjuster.

12. A hardening material for medical and dental use, in which calcium phosphate powder containing at least either one of α-tricalcium phosphate and tetracalcium phosphate is an essential component, characterised in that at least one compound of collagen and a collagen derivative and one or more of an organic acid are used as a hardening adjuster.

13. A hardening material for medical and dental use, in which calcium phosphate powder containing at least either one of α-tricalcium phosphate and tetracalcium phosphate is an essential component, characterised in that at least either one compound of tannin and a tannin derivative, either one compound of collagen and a collagen derivative, and one or more of an organic acid are used as a hardening adjuster.

14. A hardening material for medical and dental use as claimed in any one of claims 11 - 13, in which the collagen and the collagen derivative convert into fibrils under physiological conditions.

15. A hardening material for medical and dental use as claimed in claim 14, in which the collagen and the collagen derivative require a time longer than 8 minutes for conversion into fibrils under physiological conditions.

Fig. 1

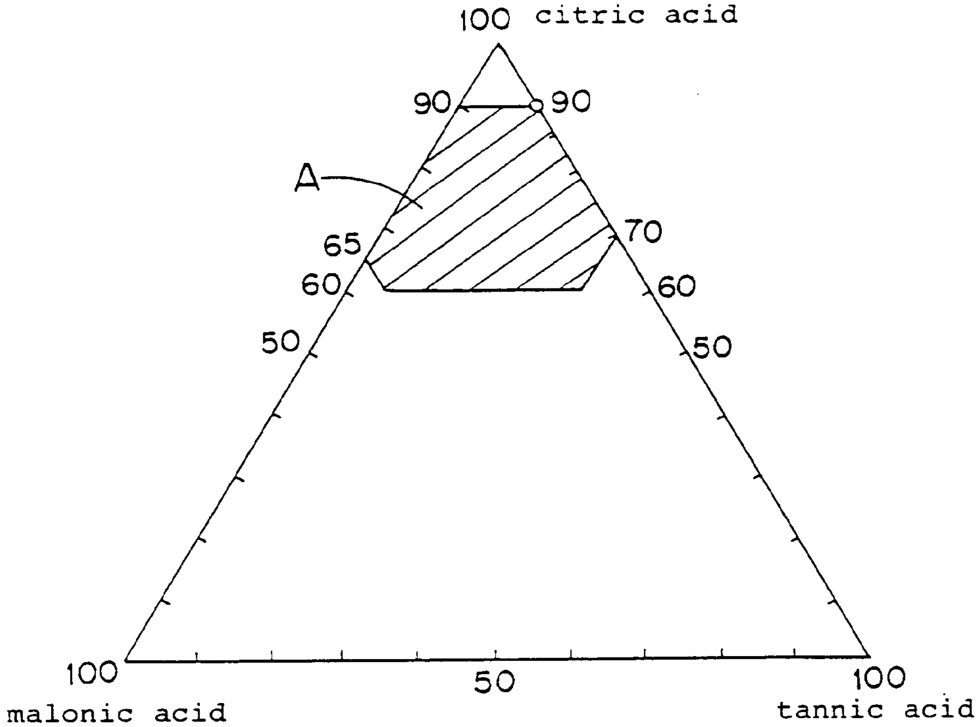

100 citric acid
90
90
A
70
65
60
60
50
50
100
malonic acid
50
100
tannic acid

Fig.2

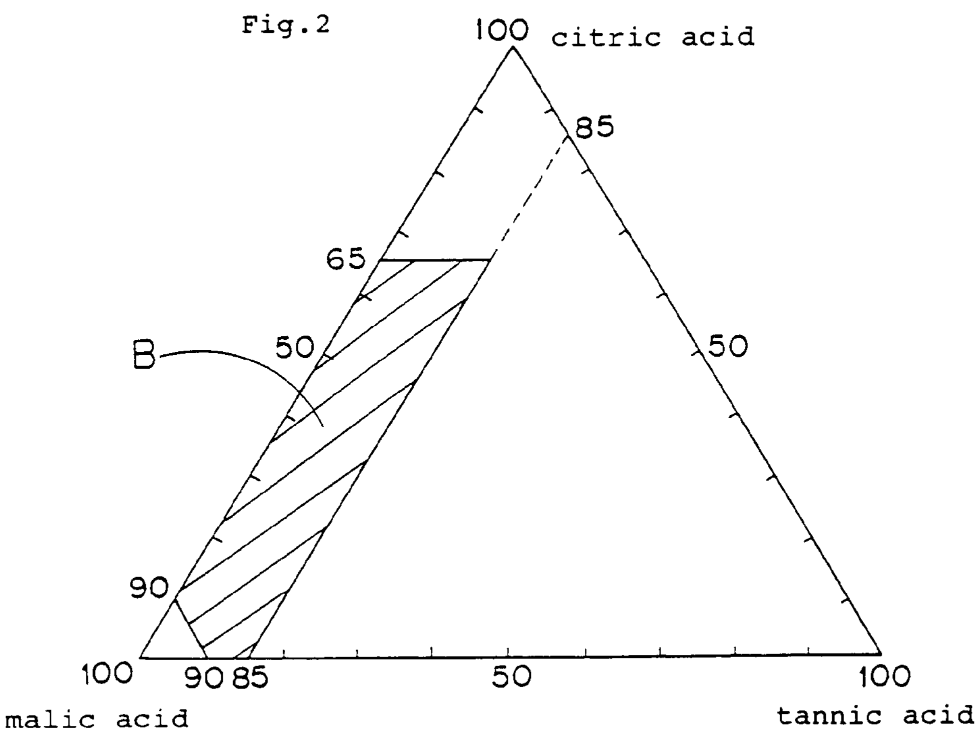

100 citric acid
85
65
B
50
50
90
100
malic acid
90 85
50
100
tannic acid

Fig. 3

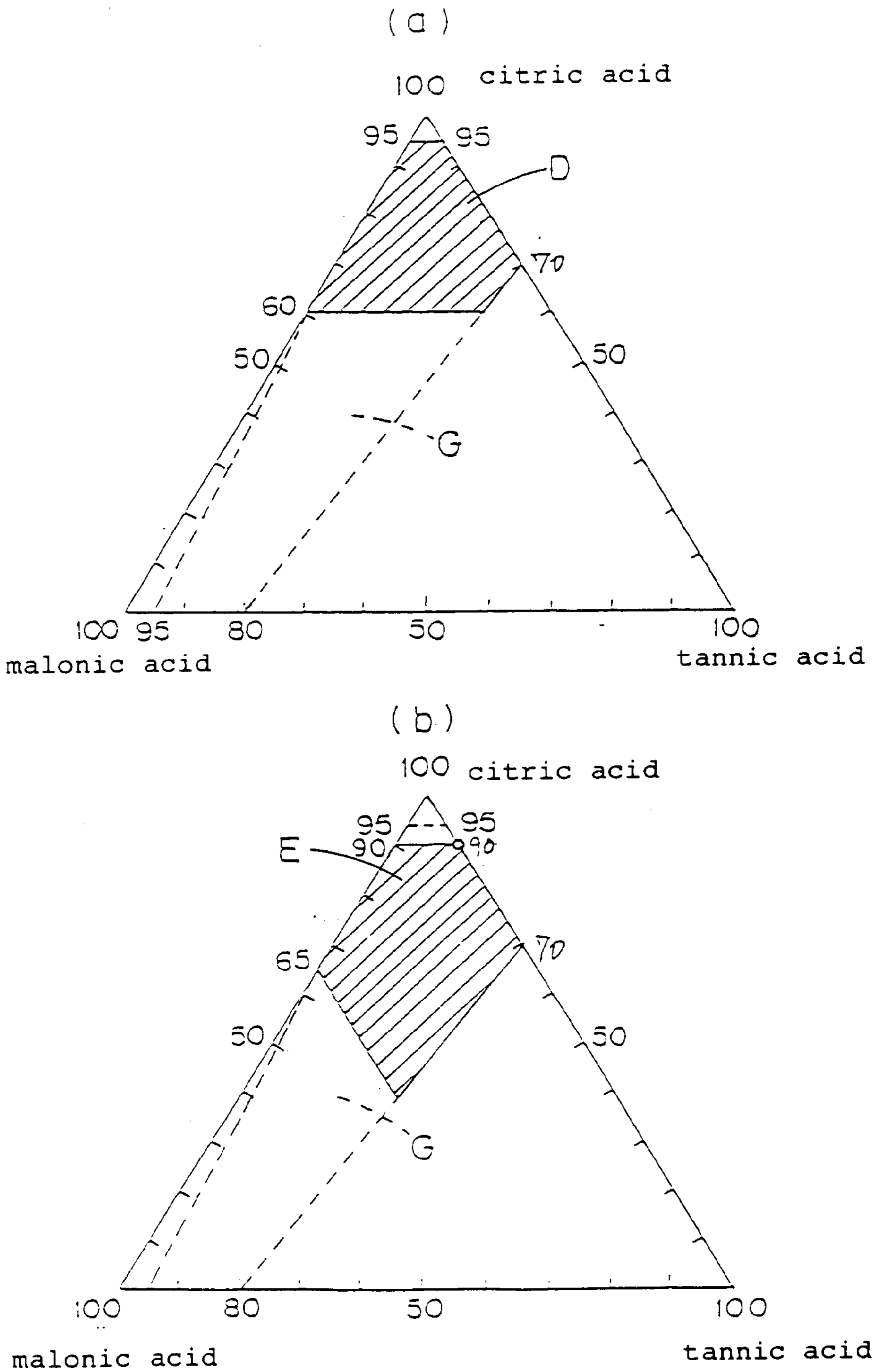

(a)
100 citric acid
95
95
D
70
60
50
50
G
100
95
80
50
100
malonic acid
tannic acid
(b)
100 citric acid
95
95
E
90
90
65
70
50
50
G
100
80
50
100
malonic acid
tannic acid

Fig. 3

(C)

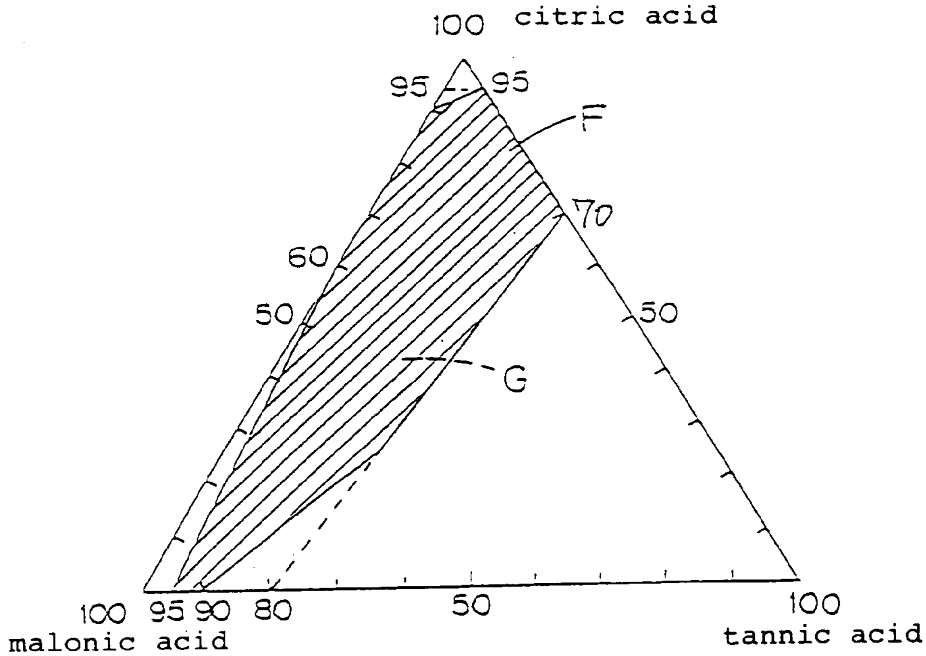

100 citric acid
95
95
F
70
60
50
50
G
100 95 90 80
50
100
malonic acid
tannic acid

Fig. 4

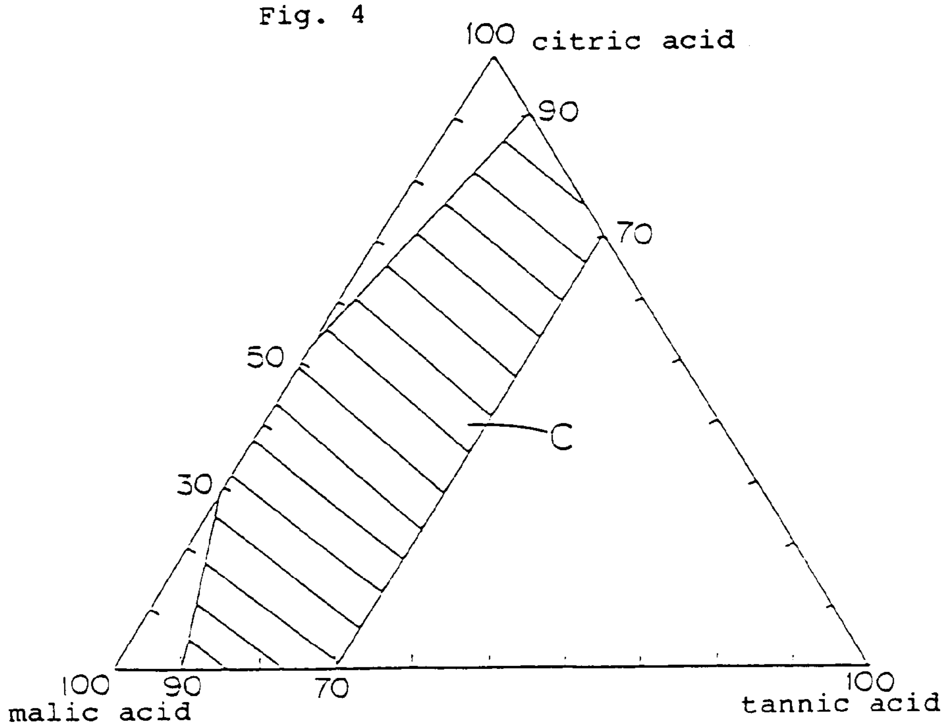

100 citric acid
90
70
50
C
30
100 90 70
100
malic acid
tannic acid

Fig. 5

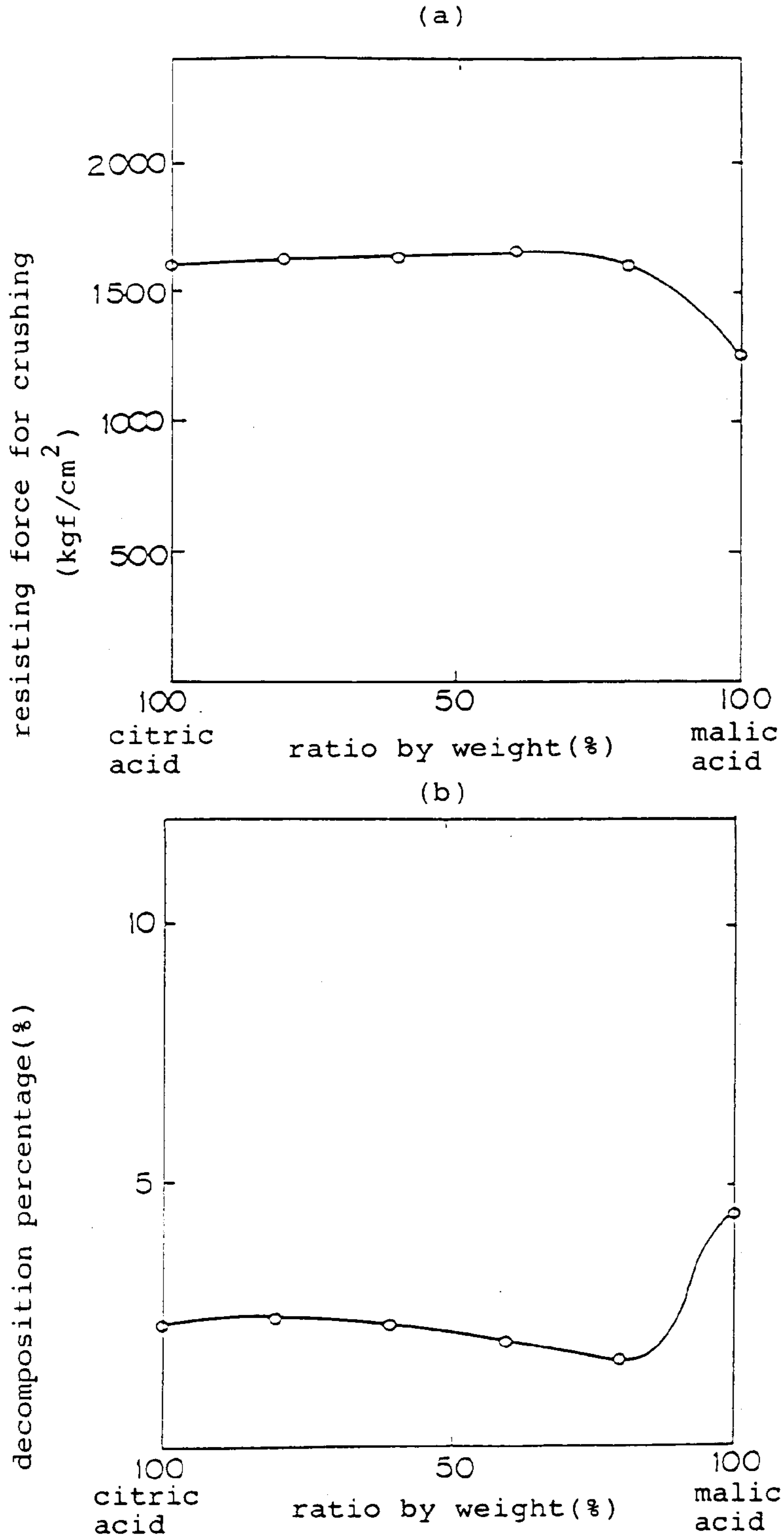

(a)
2000
1500
1000
500
resisting force for crushing
(kgf/cm²)
100
citric acid
50
ratio by weight(%)
100
malic acid
(b)
10
5
decomposition percentage(%)
100
citric acid
50
ratio by weight(%)
100
malic acid

Fig. 5
(C)

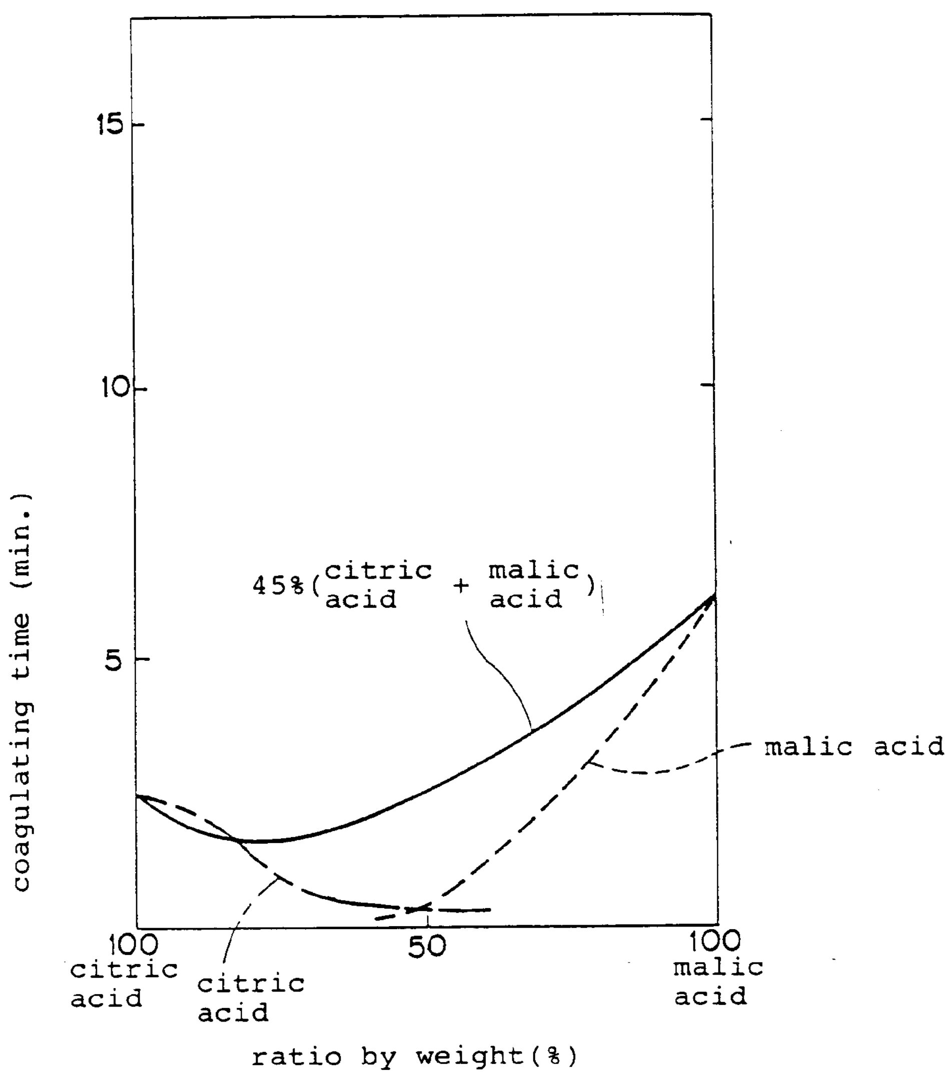

15
10
5
coagulating time (min.)
45%(citric acid + malic acid)
malic acid
100
citric acid
citric acid
50
100
malic acid
ratio by weight(%)

Fig. 6

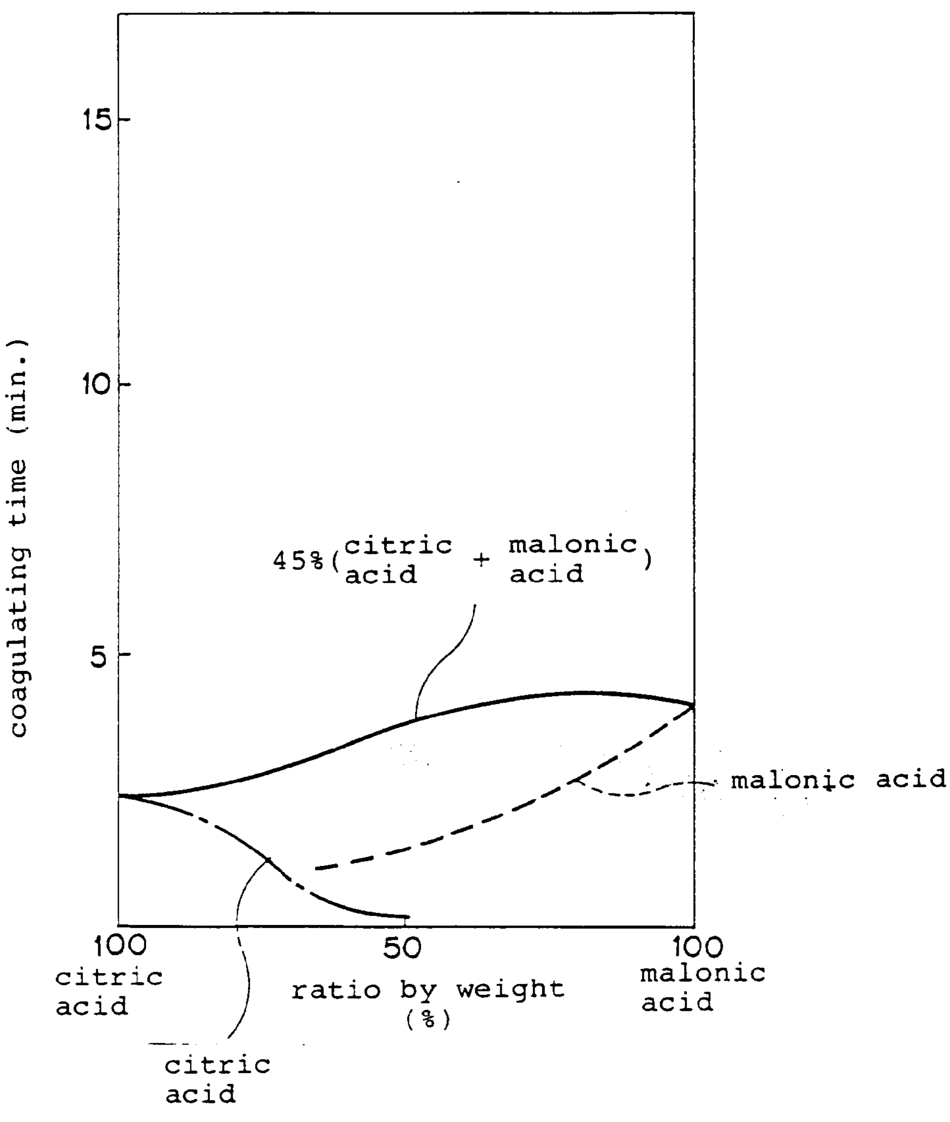
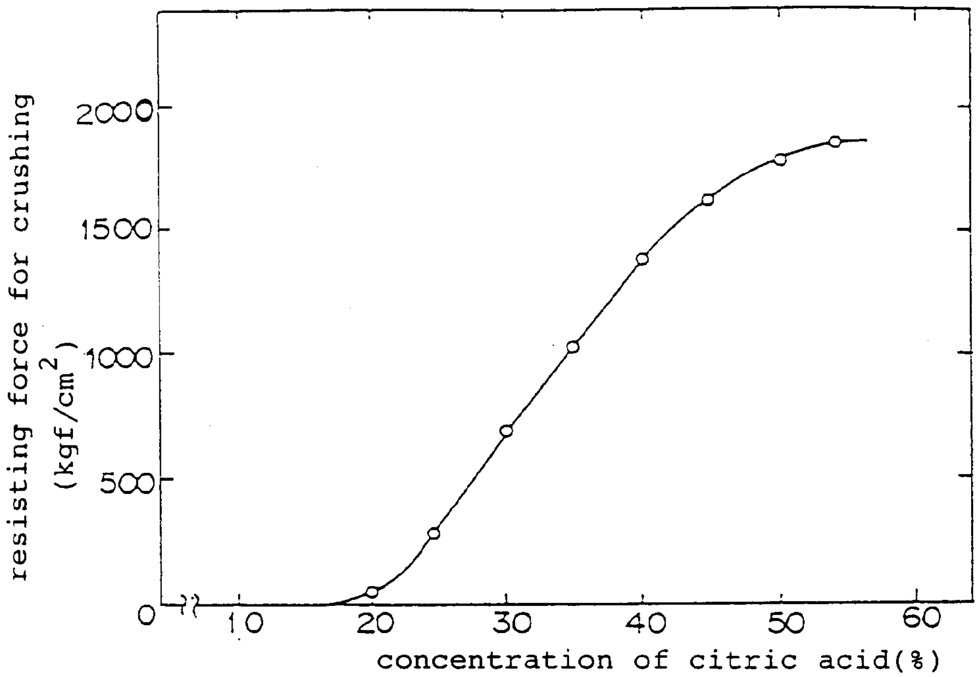

coagulating time (min.)
15
10
5
45% (citric acid + malonic acid)
malonic acid
citric acid
100 citric acid
50
100 malonic acid
ratio by weight (%)

Fig. 7
(a)


resisting force for crushing
(kgf/cm^2)
2000
1500
1000
500
0
10
20
30
40
50
60
concentration of citric acid(%)

(b)

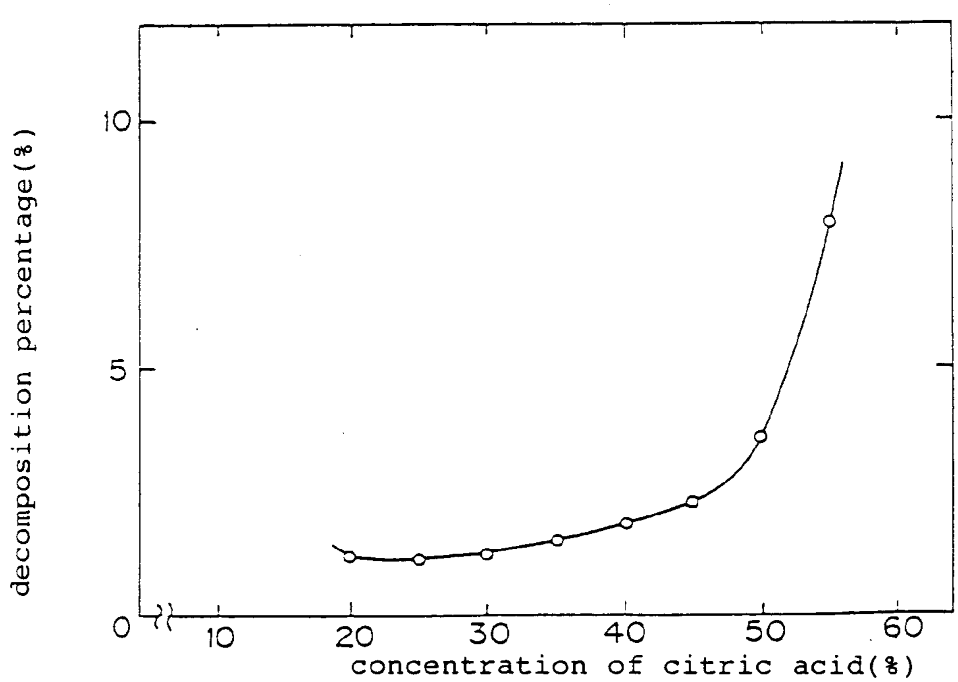

decomposition percentage(%)
10
5
0
10
20
30
40
50
60
concentration of citric acid(%)

Fig. 7

(C)

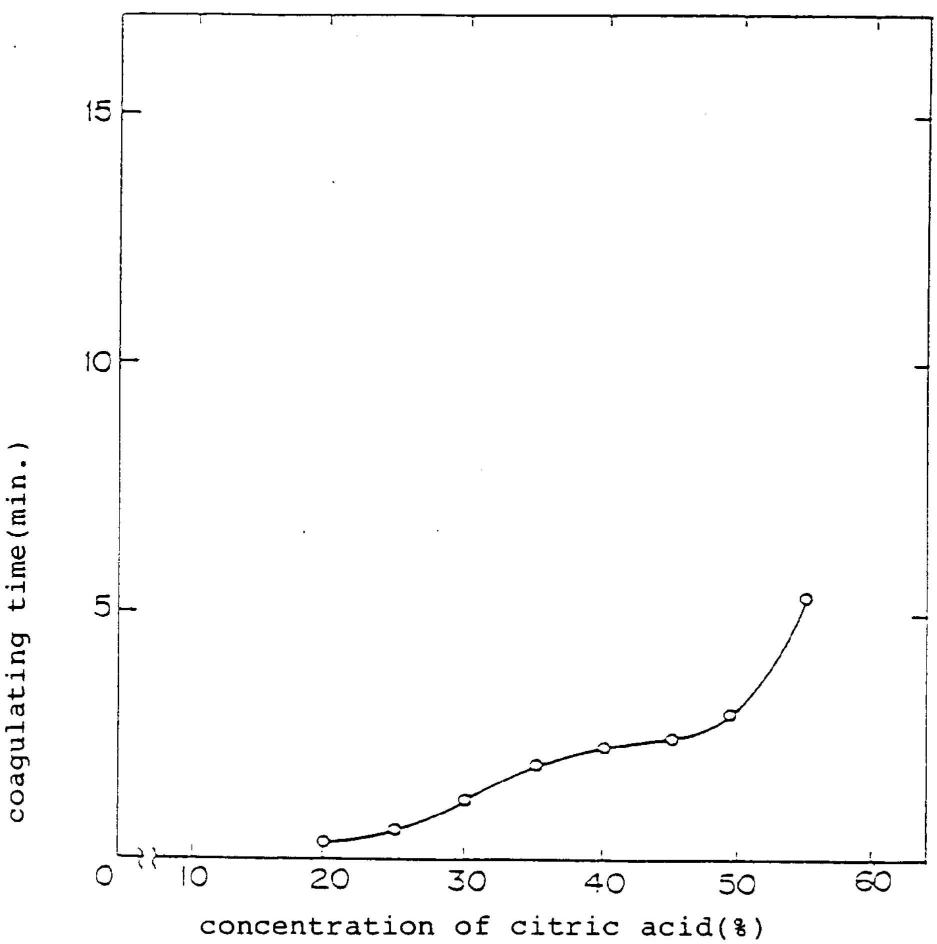

coagulating time(min.)
15
10
5
0
10
20
30
40
50
60
concentration of citric acid(%)

Fig. 8

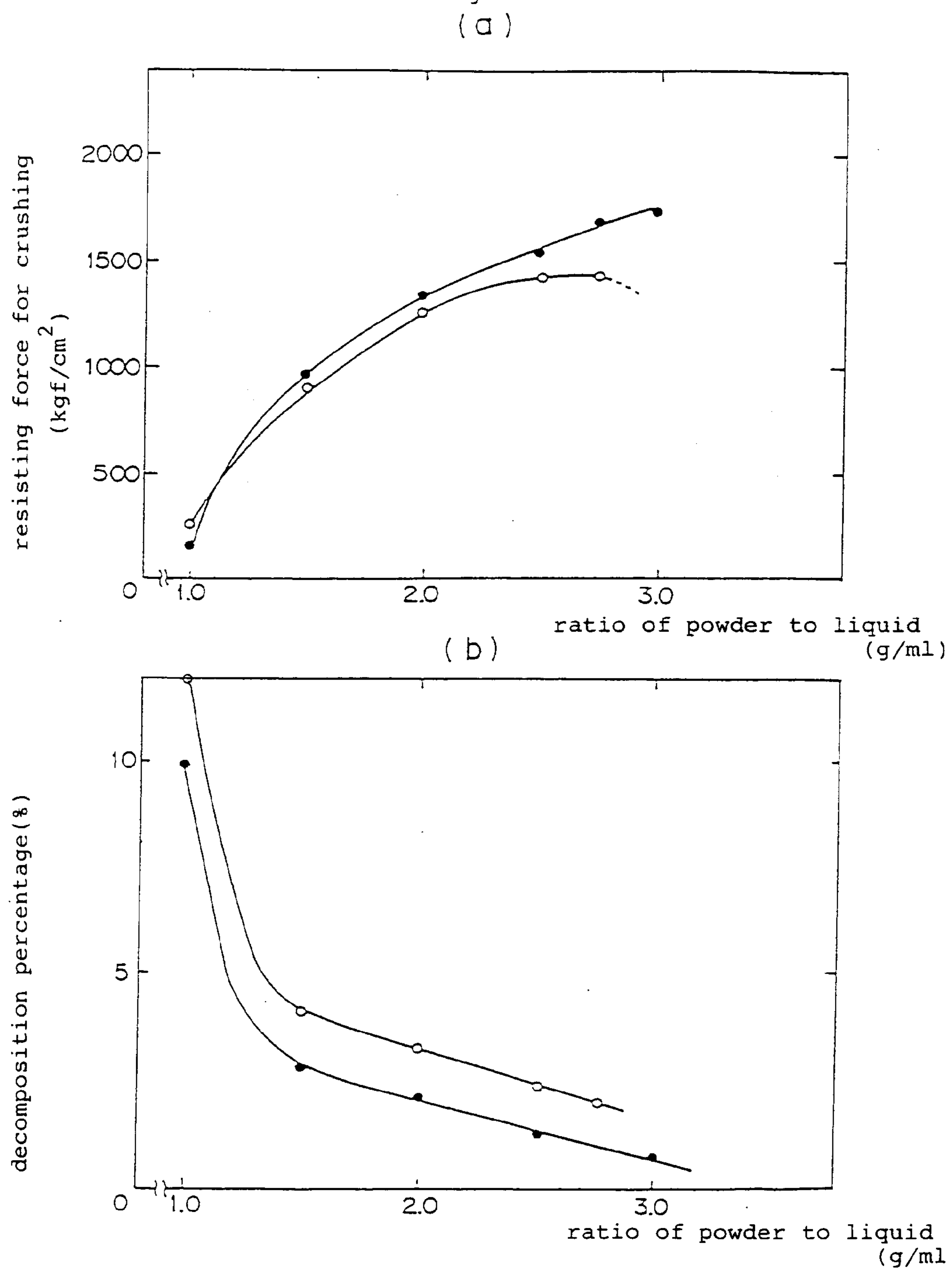

(a)
2000
1500
1000
500
0
1.0
2.0
3.0
resisting force for crushing
(kgf/cm2)
ratio of powder to liquid
(g/ml)
(b)
10
5
0
1.0
2.0
3.0
decomposition percentage(%)
ratio of powder to liquid
(g/ml)

Fig. 8

(C)

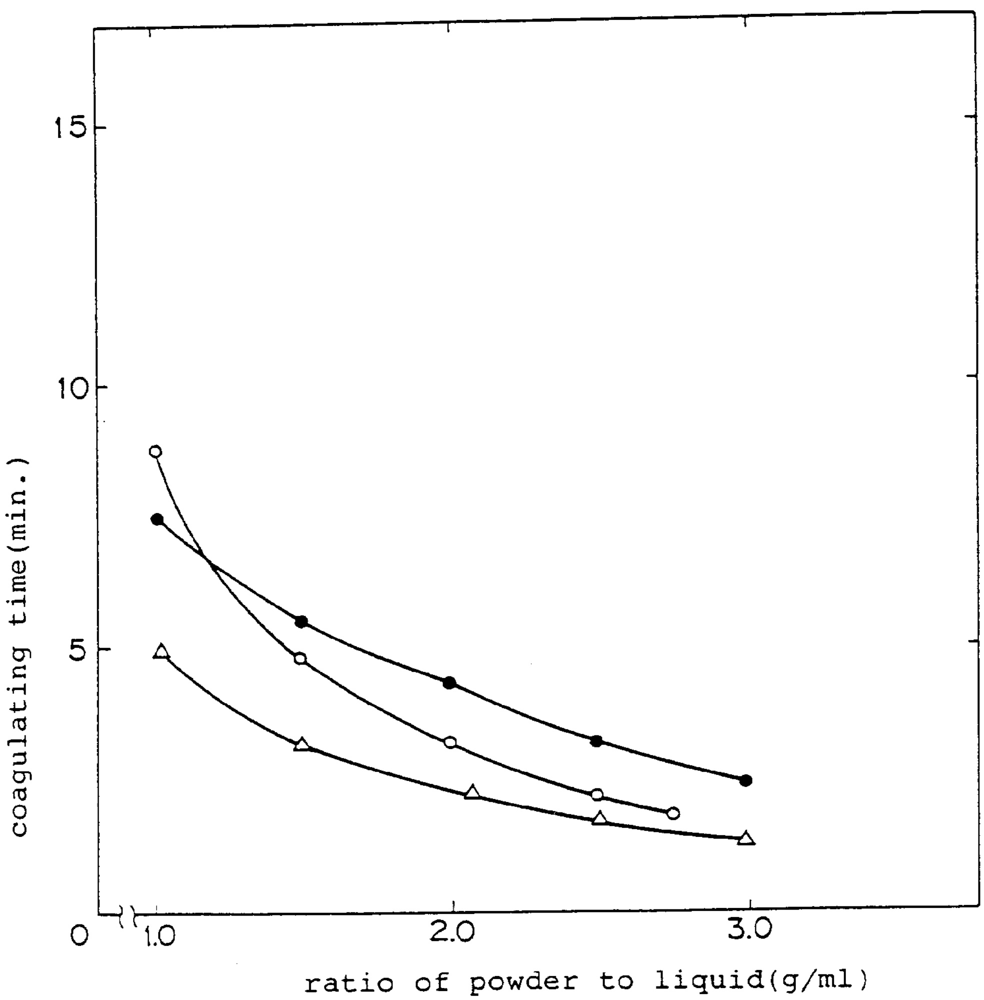

15
10
5
0
1.0
2.0
3.0
coagulating time(min.)
ratio of powder to liquid(g/ml)

Fig. 9

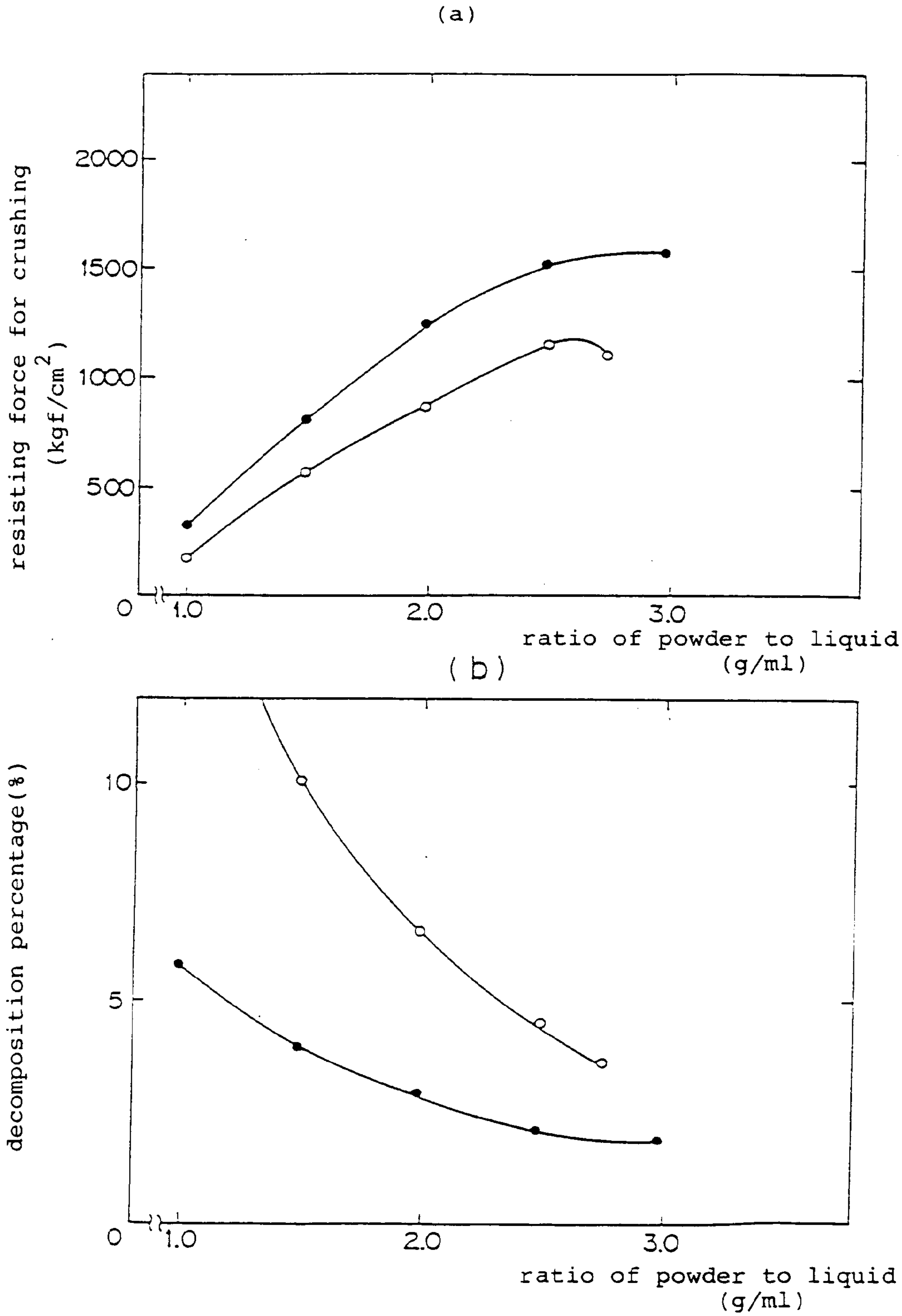

(a)
resisting force for crushing
(kgf/cm^2)
2000
1500
1000
500
0
1.0
2.0
3.0
ratio of powder to liquid
(g/ml)
(b)
decomposition percentage(%)
10
5
0
1.0
2.0
3.0
ratio of powder to liquid
(g/ml)

Fig. 9

(C)

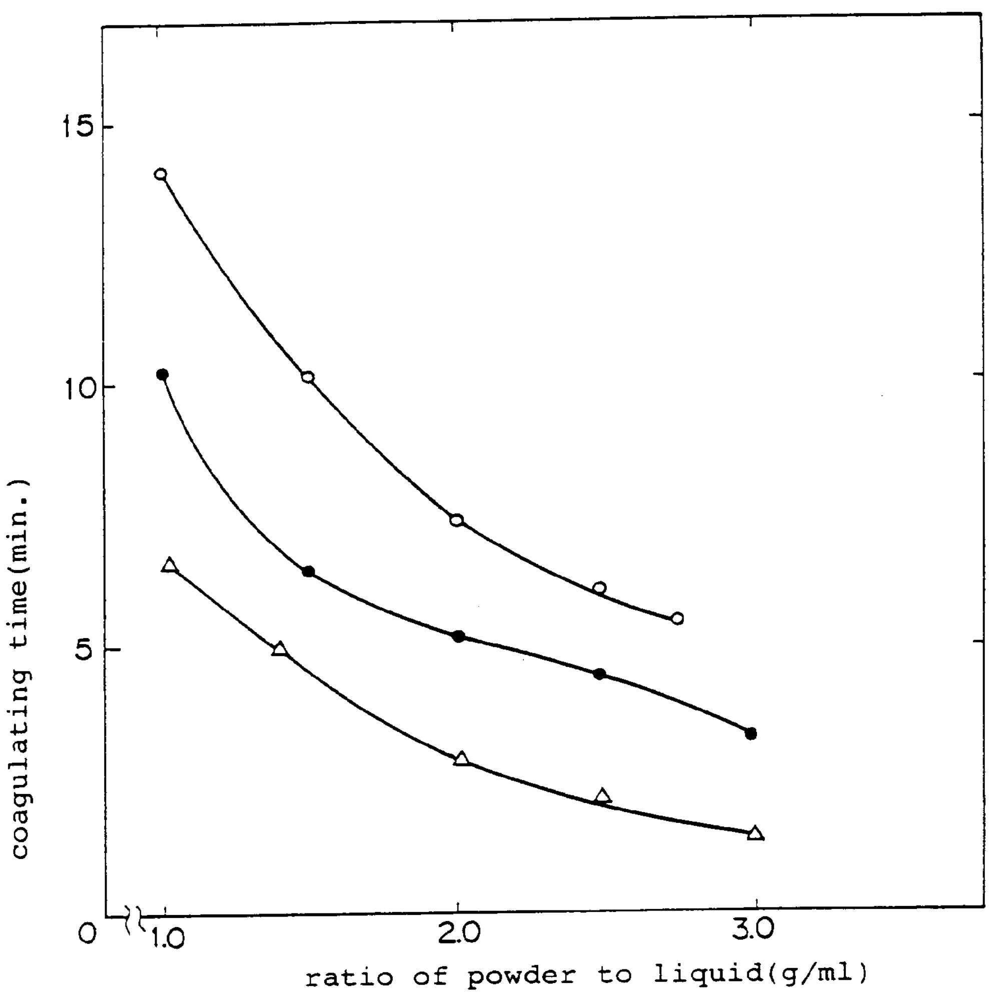

15
10
5
0
1.0
2.0
3.0
coagulating time(min.)
ratio of powder to liquid(g/ml)

Fig. 10

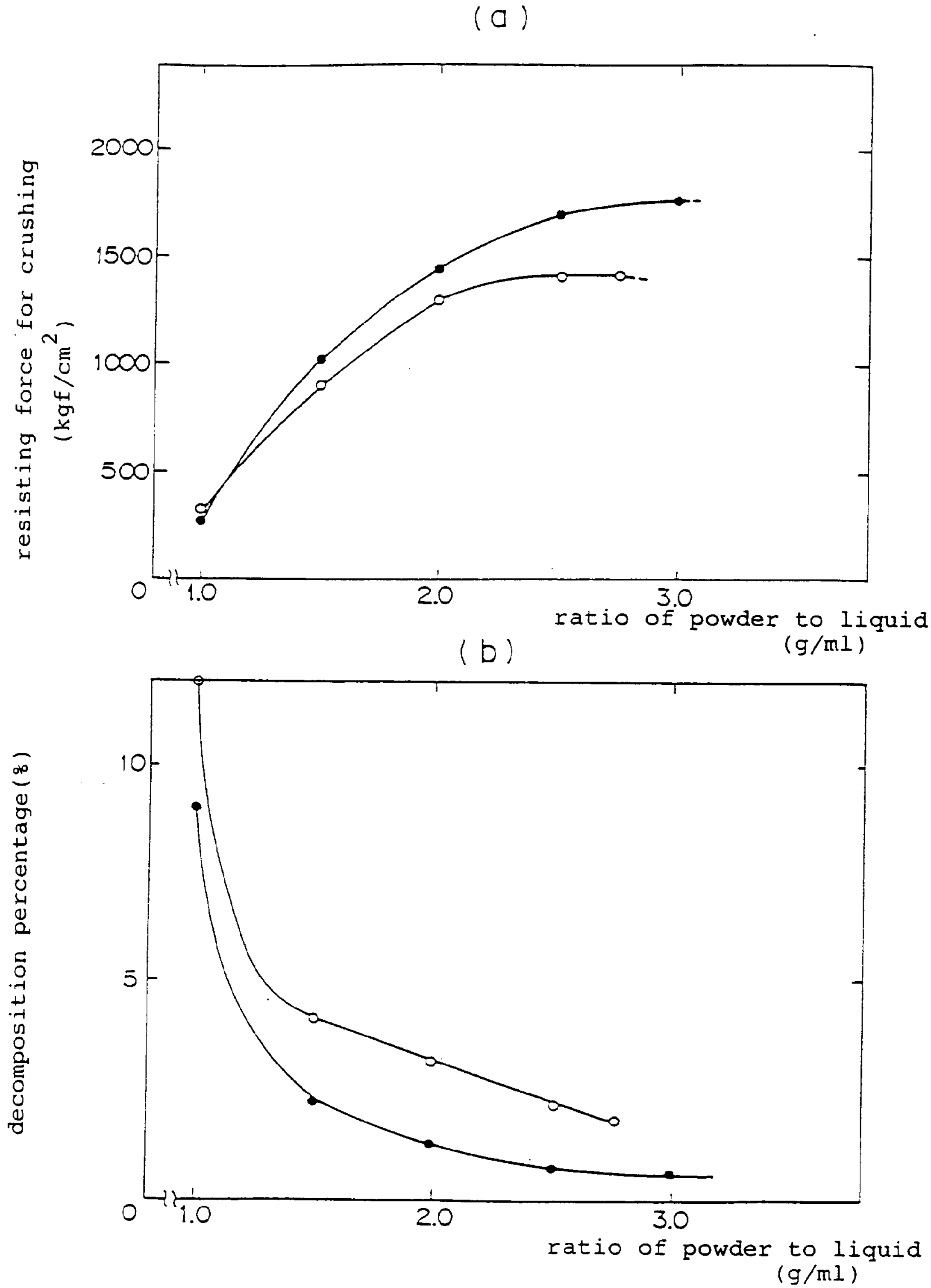

(a)
2000
1500
1000
500
0
resisting force for crushing
(kgf/cm^2)
1.0
2.0
3.0
ratio of powder to liquid
(g/ml)
(b)
10
5
0
decomposition percentage(%)
1.0
2.0
3.0
ratio of powder to liquid
(g/ml)

Fig. 10

(C)

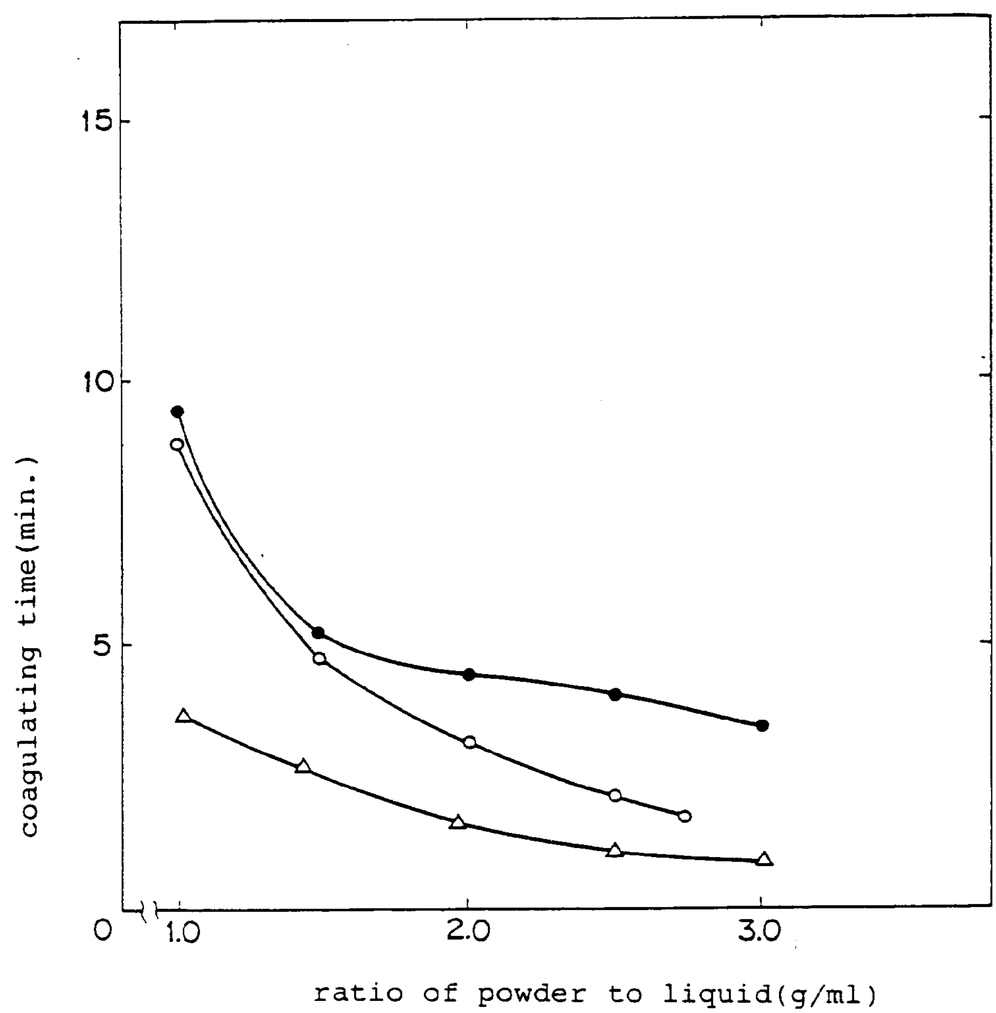

15
10
5
0
1.0
2.0
3.0
coagulating time(min.)
ratio of powder to liquid(g/ml)

Fig. 11

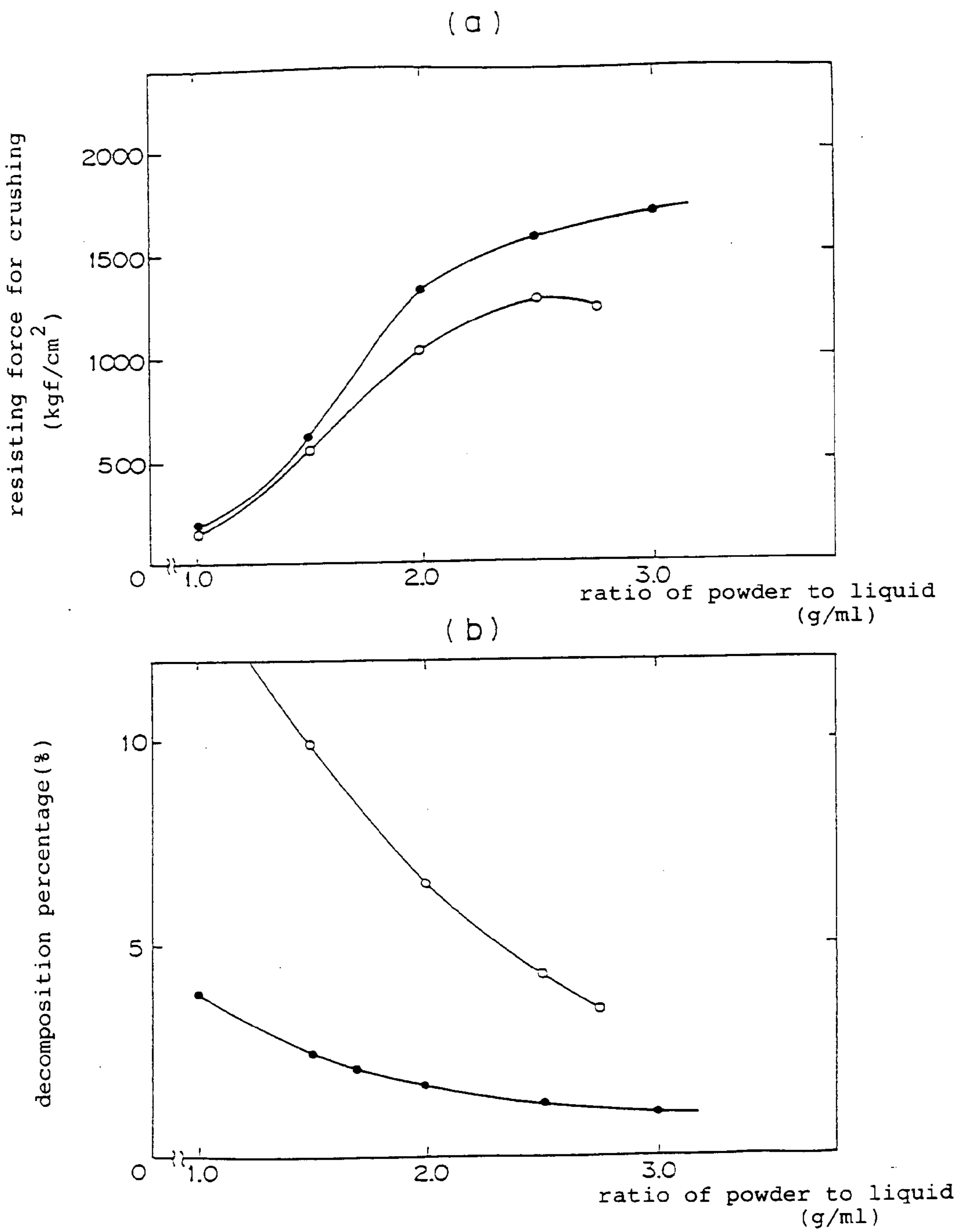

(a)
resisting force for crushing
(kgf/cm^2)
2000
1500
1000
500
0
1.0
2.0
3.0
ratio of powder to liquid
(g/ml)
(b)
decomposition percentage(%)
10
5
0
1.0
2.0
3.0
ratio of powder to liquid
(g/ml)

Fig. 11

(C)

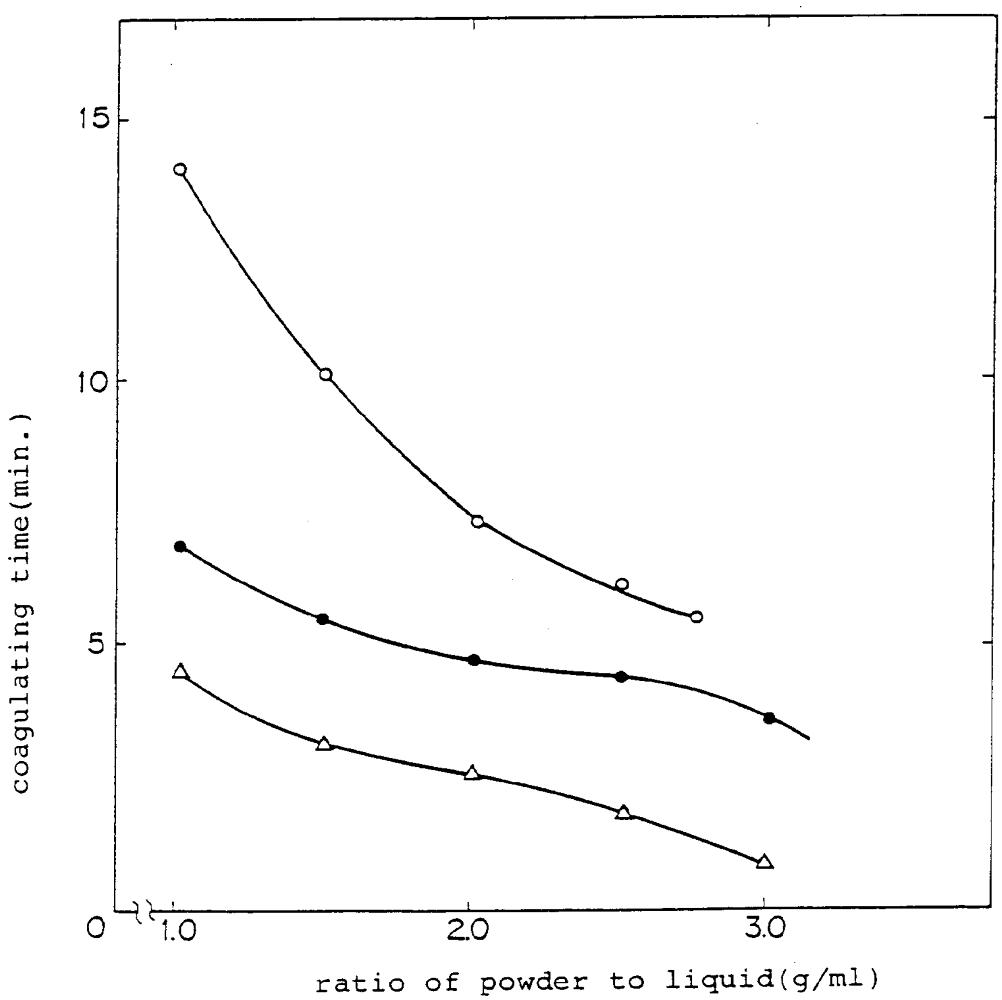

15
10
5
0
1.0
2.0
3.0
coagulating time(min.)
ratio of powder to liquid(g/ml)

Fig. 12

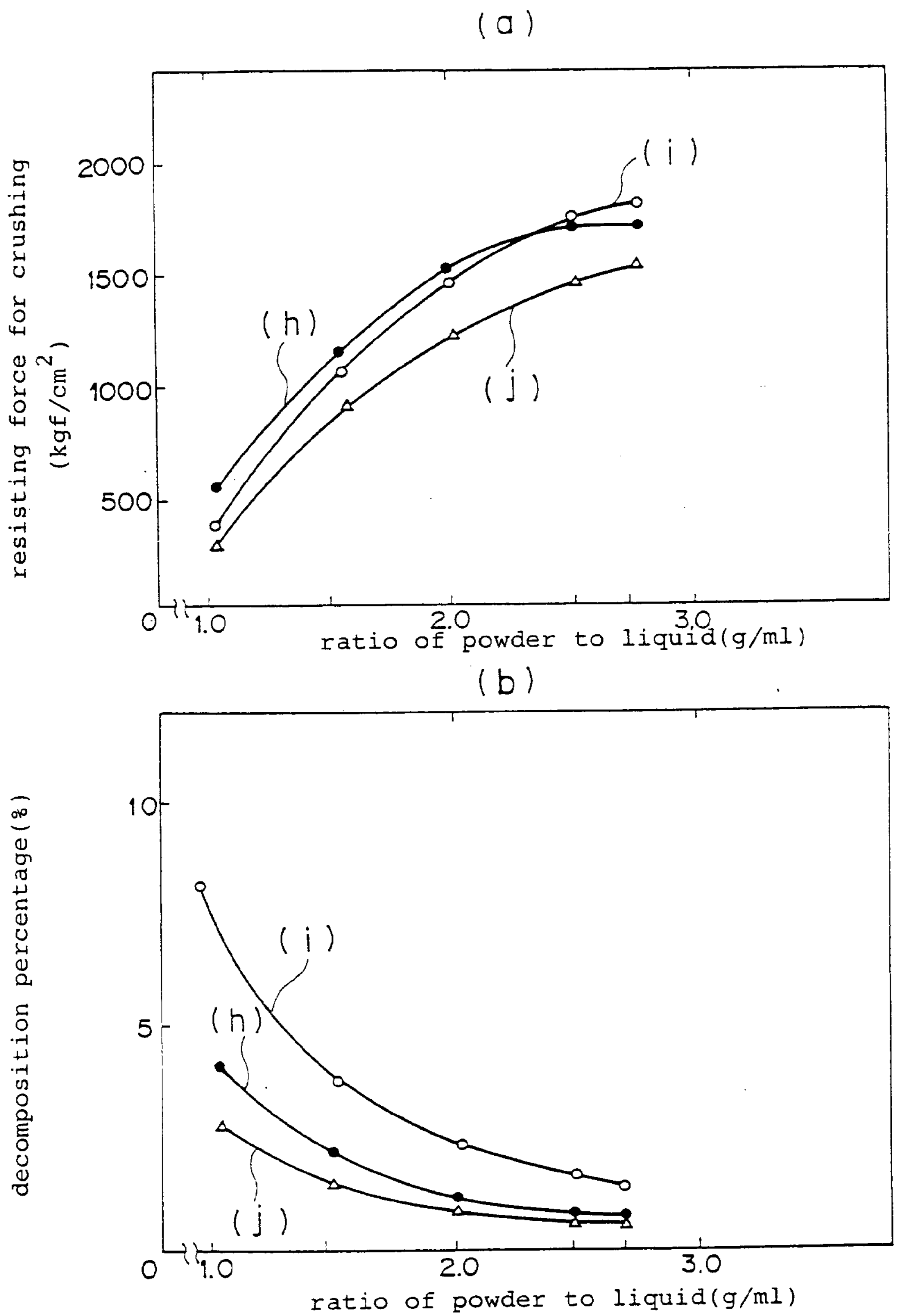
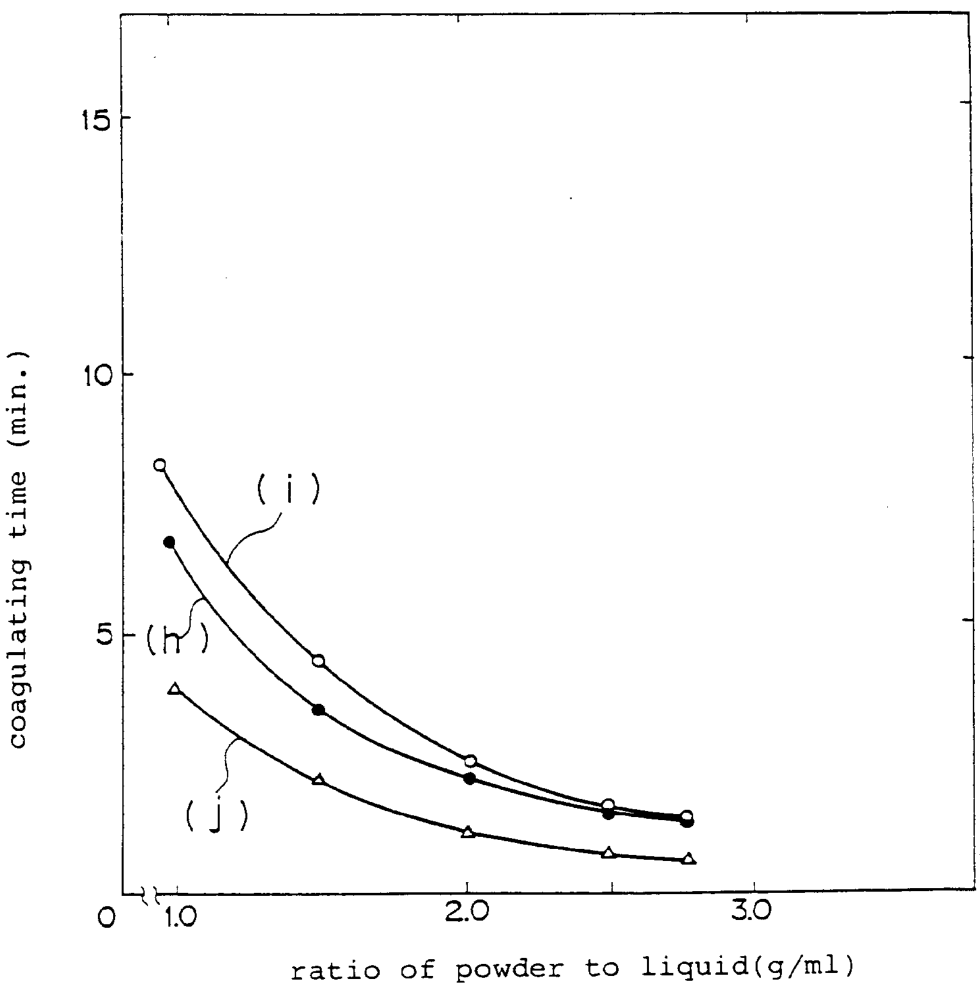

(a)
resisting force for crushing
(kgf/cm^2)
2000
1500
1000
500
0
1.0
2.0
3.0
ratio of powder to liquid(g/ml)
(h)
(i)
(j)
(b)
decomposition percentage(%)
10
5
0
1.0
2.0
3.0
ratio of powder to liquid(g/ml)
(i)
(h)
(j)

Fig. 12

(c)



15
10
5
0
coagulating time (min.)
(i)
(h)
(j)
1.0
2.0
3.0
ratio of powder to liquid(g/ml)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 12 2176

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	DATABASE WPIL Week 8801, Derwent Publications Ltd., London, GB; AN 88-004651 & JP-A-62 270 164 (ADVANCE KK) 24 November 1987 * abstract *	1-4	A61L27/00 A61K6/033 A61L25/00
X,P	DATABASE WPIL Week 8918, Derwent Publications Ltd., London, GB; AN 89-133092 & JP-A-1 076 861 (MITSUBISHI MINING CEMENT) 22 March 1989 * abstract *	1-4	
X,D	PATENT ABSTRACTS OF JAPAN vol. 9, no. 160 (C-289)4 May 1985 & JP-A-60 036 404 (MIRAI KAGAKU KENKYUUSHO KK) 25 February 1985 * abstract *	5-15	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
X,P	DATABASE WPIL Week 8933, Derwent Publications Ltd., London, GB; AN 89-23897 & JP-A-1 170 463 (HAIRU KK) 5 July 1989 * abstract *	5-15	A61L A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	23 FEBRUARY 1993	G.COUSINS- VAN STEEN

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)